Increased locoregional blood flow in brain tumors after cervical spinal cord stimulation

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Object. Patients with high-grade gliomas have poor prognoses following standard treatment. Generally, malignant brain tumors have a decreased blood flow that results in increased resistance to radiation and reduced delivery of chemotherapeutic agents and oxygen. The aim of the present study was to assess the effect of spinal cord stimulation (SCS) on locoregional blood flow in high-grade tumors in the brain.

Methods. Fifteen patients (11 with Grade III and four with Grade IV brain tumors) had SCS devices inserted prior to scheduled radiotherapy. Both before and after SCS, the patients underwent the following procedures: 1) single-photon emission computerized tomography (SPECT) scanning; 2) middle cerebral artery (MCA) blood flow velocity measurements (centimeters/second) with the aid of transcranial Doppler (TCD) ultrasonography; and 3) common carotid artery (CCA) blood flow volume quantification (milliliters/minute) based on time-domain processing by using color Doppler ultrasonography.

The indices demonstrated on SPECT scanning before SCS were significantly lower (p < 0.001) in tumor sites compared with those in peritumoral sites (32%) and healthy contralateral areas (41%). Poststimulation results revealed the following: 1) a mean increase of 15% in tumor blood flow in 75% of patients (p = 0.033), as demonstrated on SPECT scanning; 2) a mean increase of greater than 18% in systolic and diastolic blood flow velocities in both tumorous and healthy MCAs in all but one patient (p < 0.002), as exhibited on TCD ultrasonography; and 3) a mean increase of greater than 60% in blood flow volume in tumorous and healthy CCAs in all patients (p < 0.013), as revealed on color Doppler ultrasonography studies.

Conclusions. Preliminary data show that SCS can modify locoregional blood flow in high-grade malignant tumors in the brain, thus indicating that SCS could be used to improve blood flow, oxygenation, and drug delivery to such tumors and could be a useful adjunct in chemoradiotherapy.

Key Words • blood flow • tumor • transcranial Doppler ultrasonography • single-photon emission computerized tomography • spinal cord stimulation • hypoxia

Abbreviations used in this paper: CBF = cerebral blood flow; CCA = common carotid artery; CT = computerized tomography; HMPAO = hexamethylpropyleneamine oxime; MCA = middle cerebral artery; MR = magnetic resonance; PET = positron emission tomography; SCS = spinal cord stimulation; SPECT = single-photon emission CT; TCD = transcranial Doppler.
According to the metaanalysis of Overgaard and Horsman,\(^45\) improving tumor oxygenation can lead to better local tumor control and increased overall patient survival rates. Such an improvement would be desirable in tumors with ischemic areas such as high-grade tumors in the brain. In these tumors, however, radiotherapy plus carbogen breathing and nicotinamide does not increase tumor perfusion\(^1\) and instead is related to an increase in systemic toxicity.\(^41,46,55\) More favorable results were described with the use of hyperbaric chambers,\(^10,35\) but this technique is not widely available and presents considerable logistical difficulties in terms of coordinating its use close to (both physically and temporally) or during the administration of radiotherapy. Other techniques such as arterial infusion of vasoactive substances\(^1\) can be more complex and are associated with even higher rates of morbidity. Hence, the evaluation of new approaches is appropriate and necessary.

Introduced in 1967,\(^33\) SCS is a technique that has been successfully used for the treatment of ischemic syndromes such as peripheral vascular disease\(^6\) and angina pectoris\(^4,21\) as well as for vasospasm,\(^46\) paraplegia,\(^13,21\) diabetes,\(^54\) and cancer-related pain.\(^18,37\) Increased CBF in patients without cancer has been demonstrated using TCD ultrasonography,\(^39\) inhaled \(^133\)Xe washout technique,\(^55\) SPECT scanning,\(^38\) and, more recently, functional MR imaging\(^35\) and PET scanning.\(^27\) To date, however, there have been no investigations on the effect of increased CBF on tumor blood flow. In preliminary studies in which we had used cervical SCS in patients with cancer and PO\(_2\) measurements with polarographic probes, we have demonstrated that SCS can increase tumor oxygenation in advanced tumors of the head and neck and in high-grade gliomas.\(^15\)

The aim of this prospective nonrandomized study was to assess the effect of cervical SCS on locoregional blood flow in high-grade malignant tumors in the brain.

**Clinical Material and Methods**

**Patient Population**

During a period of 48 months, 15 patients with histologically demonstrated high-grade malignant tumors of the brain (11 Grade III\(^\text{‡}\) tumors and four Grade IV\(^\text{‡}\) were recruited for this study following referral to our hospital. There were 10 men and five women, who were between the ages of 26 and 73 years (mean 50 years). For entry into the study, the patients were required to be at least 18 years of age and to have a Karnofsky Performance Scale score greater than 70. Fully informed consent was obtained from all patients and the study protocol had previously been approved by the Institutional Ethical Committee. Blood flow assessment was performed after biopsy or surgery and before scheduled radiotherapy. Later in the study, SCS was applied during the course of the radiotherapy plus chemotherapy (Tegafur, an oral prodrug of 5-fluorouracil, or hydroxyurea; Table 1). Before and after stimulation, locoregional blood flow assessments were initially performed using TCD ultrasonography and SPECT scanning; subsequently, the newer technique of CCA blood flow volume quantification with the aid of color Doppler ultrasonography was incorporated into the study protocol. Hemoglobin concentrations were recorded, but data concerning parameters related to the cardiac or systemic vasoactive response were not collected.

**Spinal Cord Stimulation**

Neurostimulation was performed using a Medtronic sys-
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tem (Medtronic Neurological, Minneapolis, MN). A tetrapolar electrode (Pisces-Quad; Medtronic Neurological) was percutaneously inserted following administration of a local anesthetic agent. An electrode was placed on the posterior or surface of the spinal cord at C2–4, in the epidural space and slightly displaced toward the tumorous side. An external or subcutaneous impulse generator provided an adjustable range of pulse width, intensity, and frequency of stimulation. Correct positioning and function were verified by inducing mild paresthesia in the upper limbs on test stimulation. Following the placement of the electrode, the SCS device remained in the off position until radiotherapy was begun, unless blood flow measurement techniques were performed. During radiotherapy, the SCS device was switched on (activated) during the day and switched off (deactivated) at night. The parameters of the stimulator were set at 1 to 3 V, a pulse width of 200 μsec, and a rate of 80 to 100 Hz.

Single-Photon Emission CT

The blood flow measurements during SPECT scanning were obtained 10 minutes after intravenous administration of 740 MBq of \(^{99m}\)Tc-HMPAO. This radiopharmaceutical agent is capable of crossing the blood–brain barrier and its intracranial distribution is proportional to blood flow. The SPECT measurements were performed with the aid of two different devices. The device used initially was a tomocamera (Orbiter; Siemens AG, Munich, Germany) equipped with a high-resolution collimator. The mode of image acquisition was the step-and-shoot system at 64 angles and a 0.12 cm^3 pixel of 6 mm thickness. These sections were identified in the standard plane (sagittal and coronal), with a two-pixel thickness. These sections were identified in the standard manner of 3 × 3 pixels of regions of interest in the cerebellum, tumor area (or tumor bed if total resection), healthy contralateral area (the same anatomical area of the cerebral hemisphere opposite to the tumor area), and peritumoral area (peripheral cerebral zone around the tumor area). Semi-quantitative indices were obtained in these areas by using the cerebellum as a reference.

After the basal SPECT measurements were obtained, the SCS device was turned on and the poststimulation SPECT measurements were performed 1 to 3 weeks later. In the course of changing from the first to the second device for SPECT scanning, studies could not be performed in two patients. Hence, a total of 13 of 15 patients underwent pre- and poststimulation studies before radiotherapy. Further, in one of these 13 patients the SPECT analysis following stimulation had been conducted incorrectly and a repetition of the measurement before beginning the scheduled radiotherapy was impossible. Thus in this patient, the pre-SCS values obtained using SPECT scanning, but not the post-SCS ones, were used in the statistical analyses.

Transcranial Laser Doppler Velocimetry

Transcranial Doppler ultrasonography of the MCA was performed via the transtemporal approach with a 2-MHz probe (Angiodine-2 Fluo-Link 300 device; DMS, Montpellier, France). In each patient TCD ultrasonography was conducted before SCS and between 1 and 10 minutes after SCS. Both measurements were obtained on the same day, after surgery and before beginning radiotherapy. The absence of stenosis was confirmed while the patient was alert, relaxed, and seated. The insonation angle was less than 60°. The TCD ultrasonography measurements in the MCA were bilateral and included systolic and diastolic velocities (centimeters/second) together with pulsatility and resistance indices. All of these measurements were conducted by the same radiologist to minimize interobserver variability. Recordings during at least three cardiac cycles were noted once an optimal stable flow image had been obtained. Each assessment was recorded at least three times to preclude operator or technical inaccuracy, and median values were used for the purpose of statistical analyses. In three of 15 patients the location of an ultrasonic window to perform the measurement was impossible so that data from only 12 patients were available for this aspect of the study.

Common Carotid Artery Volume and Blood Flow Quantification

This technique allows for a quick and noninvasive evaluation and quantification of CCA blood flow. It is based on time-domain processing and performed using a color Doppler unit (Philips Ultrasound P-800; Philips, Irvine, CA). In each patient, the measurements were performed on the same day, before and between 1 and 10 minutes after SCS. Both measurements were obtained on the same day, both after surgery and before beginning radiotherapy. The absence of significant stenosis in extracranial CAs was confirmed while the patient was alert, relaxed, and supine. A 7.5-MHz linear high-definition probe with a Doppler angle less than 60° was used. All studies were conducted by the same radiologist to minimize interobserver variability. When an optimal and stable flow image was obtained, recordings were taken during at least three cardiac cycles. Each measurement was recorded at least three times to reduce inaccuracy, and the median value was used in the statistical analyses. In the eight patients assessed, we obtained information on the blood flow volume (milliliters/minute) of both CCAs 2 cm or larger, before the carotid bifurcation. Although not an objective within our study protocol, we evaluated the overall survival rate in our series of patients.

Statistical Analysis

Commercially available software (SPSS for Windows, version 7.0; SPSS-Íberica, Madrid, Spain) was used throughout this study. The distribution of the data was assessed using the Kolgomorov–Smirnov test. The two-tailed paired t-test was used to compare values measured before and after measurements were made using SCS and to compare values obtained in two different cerebral areas in the same patient. The one-way analysis of variance test was calculated to
compare data collected before SCS from among tumorous, peritumoral, and healthy contralateral areas. Continuous data are expressed as the mean ± standard deviation. The Pearson r test was used for correlation analysis. All probability values less than 0.05 were considered to be statistically significant.

Results

Single-Photon Emission CT Index

The SPECT indices obtained before stimulation were 0.79 ± 0.05 in the healthy contralateral area, 0.69 ± 0.11 in the peritumoral area, and 0.47 ± 0.16 in the tumor. The mean index in the tumor site was 41% lower than that in the healthy contralateral area (p < 0.001) and 32% lower than that in the peritumoral area (p < 0.001); the index measured at the peritumoral area was 13% lower than that at the healthy contralateral site (p = 0.006). In comparing these three areas by calculating the one-way analysis of variance, we noted that these differences were statistically significant (p < 0.001; Fig. 1).

The SPECT indices demonstrated after SCS were 0.79 ± 0.08 in the healthy contralateral area, 0.73 ± 0.14 in the peritumoral area, and 0.54 ± 0.19 in the tumor. After SCS, the SPECT index increased in 75% of tumors. There was a mean increase of 15% in the index at the tumor site (p = 0.033; Fig. 1), with no significant modification of the indices at the peritumoral or healthy contralateral areas. Figure 2 depicts SPECT images obtained in a representative patient before and after SCS.

Transcranial Doppler Ultrasonography Measurements

There was a significant increase (p < 0.002) in systolic and diastolic blood flow velocities after SCS in tumorous and healthy MCAs in all but one patient. On the tumorous side, systolic blood flow velocity increased by a mean of 19% (from 88 ± 24 to 105 ± 27 cm/second; p = 0.002) and diastolic blood flow velocity increased by a mean of 18% (from 39 ± 14 to 46 ± 13 cm/second; p = 0.002; Fig 3). Resistance and pulsatility indices did not change significantly following SCS.

Carotid Artery Blood Flow Volume Quantification

Blood flow volume was increased after SCS in tumorous and healthy CCAs in all patients. On the tumorous side, the mean increase was 61% (from 205 ± 61 to 331 ± 108 ml/minute; p = 0.009). On the healthy side, the mean increase was 74% (from 218 ± 87 to 378 ± 202 ml/minute; p = 0.013; Fig. 4).

No significant correlation between hemoglobin levels and any of the evaluated parameters was found in the overall study group.

Table 1 contains a summary of individual percentage changes after SCS in the SPECT index (in the tumor); systolic and diastolic blood flow velocities in the MCA (on the tumorous side); and CCA blood flow (on the tumorous side).

Patient Survival

Patient survival was inversely correlated with patient age (r = −0.728, p = 0.002). Furthermore, patient survival with respect to tumor grade was 28 ± 7 months for those with Grade III tumors and 9 ± 2 months for those with Grade IV tumors.

FIG. 1. Bar graph demonstrating SPECT indices with respect to the cerebellum. Measurements obtained before SCS (shaded bars) at the site of the tumor and peritumoral areas revealed lower perfusion than that in healthy contralateral areas (p < 0.001). A mean increase of 15% in the SPECT index was seen in tumor areas (white bar; p = 0.033). Error bars show the 95% confidence interval (CI).

FIG. 2. Case 11. Axial (left), coronal (center), and sagittal (right) images obtained in a patient after a subtotal resection of a right frontotemporal glioblastoma. The SPECT scans were obtained before (upper) and after (center) SCS. Lower: Magnetic resonance images obtained in the same patient. The SPECT indices before and after stimulation in the right frontal lesion were 0.47 and 0.57, respectively (21% increase), and 0.85 and 0.92, respectively (8% increase), in the healthy area. On SPECT scanning performed after SCS, we noted a general increase in perfusion of the entire brain, a persistent minor perfusion of the tumor and peritumoral region (front, right) compared with the healthy contralateral region (front, left), and a decrease in the difference in perfusion between the tumor site and the peritumoral area compared with other areas of the brain.
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Fig. 3. Bar graph demonstrating blood flow velocities in the MCA on the tumor side both before (shaded bars) and after (white bars) SCS. Systolic blood flow velocities are compared and show a 19% increase (p = 0.002). Diastolic velocities are compared and show an 18% increase (p = 0.002). Error bars indicate the 95% CI.

Fig. 4. Bar graph demonstrating blood flow velocity quantification in the CCA (measured in milliliters/minute) of the tumor and on the healthy side. Blood flow velocity was increased in all patients, with an overall increase greater than 60% bilaterally (p < 0.013). Error bars show the 95% CI.

Discussion

Malignant tumors in the brain generally have a higher percentage of hypoxic areas and lower perfusion than normal cortex. Confirming these observations are data from a previous report in which we measured PO2 by using polarographic probes together with pre-SCS SPECT scanning data from the present study in which we demonstrated a 32% lower index in the tumor compared with that in peritumoral areas and significantly lower indices than in the preceding areas compared with those in healthy contralateral areas.

The SPECT measurements obtained after stimulation showed a 15% blood flow increase in the tumor. Spinal cord stimulation seems to be a promising means of increasing tumor blood flow, and our results compare favorably with those in other studies in which a lack of perfusion enhancement (with the aid of HMPAO-SPECT scanning) following the administration of nicotinamide and carbogen in patients with glioblastomas has been reported. Although 75% of patients in our study showed some degree of increase in blood flow, there was considerable variation in this response among patients. The SPECT scanning index reflects the ratio between the affected zone and the cerebellum, the area in which the blood flow has a greater increase following SCS. Hence, a real increase in tumor perfusion, which might be lower than that occurring in the cerebellum, could appear as a diminution of the SPECT scanning index (25% of patients). Other factors, such as differences in the glutathione concentration in the tumor, could also play a role in interpatient differences in the uptake of contrast medium.

Cerebral arteries have relatively constant diameters during assessment by TCD ultrasonography. It is assumed that changes in MCA blood flow velocity correlate inversely with changes in vessel resistance and are related to changes in the diameter of cerebral arterioles. Hence, changes in MCA blood flow velocity demonstrated on TCD studies correlate with changes in CBF. Transcranial Doppler ultrasonography measurements following SCS in patients without cancer have demonstrated increased blood flow velocities in MCAs. In the present study, patients with brain tumors also show this effect on both the healthy and the tumor side. The increase in systolic (19%) and diastolic (18%) blood flow velocities in the tumor is close to the 15% observed in SPECT in the tumor after SCS. These findings indicate that blood flow increases in the tumor, which are produced by SCS, could be caused by a decrease in peripheral vascular resistance in tumorous areas in these patients. An increment in the locoregional flow of between 15 and 20%, as demonstrated in our SPECT scanning and TCD ultrasonography data, can appear modest but the clinical repercussions could be very considerable. For example, in a previously described report we presented measurements of tumor PO2 obtained before and after SCS (with the aid of a polarographic probe system) in two different tumor areas in each of three patients included in the current study. During SCS, tumor PO2 increased significantly in five of six tumor areas (mean increase 40%), and the fraction of hypoxic values less than 10 mm Hg and 5 mm Hg was decreased by a mean of 40%. This indicates that the improvement in oxygenation occurred in those areas in which it was most required. Even more important than this absolute increase is the observation that, based on the cellular radiosensitivity curve as a function of oxygenation, very small increases in PO2 (even 2–4 mm Hg) in the most hypoxic cells can induce a marked increase in the effect of any administered radiation.

As with SPECT scanning, TCD ultrasonography is a semiquantitative technique. Hence, a quantification of CCA blood flow volume using time-domain Doppler ultrasonography was incorporated into the study once this procedure became available. This technique simultaneously evaluates blood flow velocity and vessel diameter, and data have been presented in milliliters per minute. The usefulness and validity of this technique have been described previously. In our eight patients, the method demonstrated a bilateral CCA blood flow increase greater than 50% after SCS, despite the small number of patients studied and the considerable variability observed in the measurements. The considerable increase demonstrated after SCS, although somewhat surprising, has been described previously in animal studies of both the internal CA and the CCA, and the data...
are in agreement with those in our preliminary studies of SCS in patients with advanced head and neck tumors.12 A few minutes after SCS activation, Doppler measurements in CCAs and MCAs increased in all but one patient. This suggests a rapid and consistent effect. The considerable magnitude of the increase demonstrated (50 and 18%, respectively) prognosticates its potential clinical usefulness.

Hence, on the tumor side during SCS, blood flow increases in CCAs and on TCD ultrasonography studies appear to be accompanied by increases in SPECT indices in tumors (further explanations are proposed later). On the healthy side in the patient, however, similar blood flow increases in the CCA and on TCD ultrasonography were not followed by increases in the SPECT index. As mentioned earlier, this may be due to the fact that SPECT indices are expressed as a ratio between the area studied and the cerebellum. As such, healthy tissues with an increase similar to that in the cerebellum do not appear as variations in the SPECT indices. Additionally, the capacity for vascular self-regulation in healthy tissue can limit the magnitude of blood flow in healthy tissues compared with that in tumor tissues, which have limited or absent self-regulatory capacities.56

Spinal cord stimulation does not induce claustrophobia, as does hyperbaric ventilation, and is associated with low rates of morbidity and side effects (~ 10%),7,18 characteristics especially important when the procedure is compared with many other adjuvant therapies used in treating cancer. Data from this study showed that SCS could be safely conducted in selected patients with brain tumors and that it was possible to incorporate this additional method within a chemoradiotherapy schedule without an increase in the incidence of any major side effects. Note that it was necessary to remove the electrodes in four patients before completion of the planned treatment. In two of these patients (13%) there was a local infection along the trajectory of the subcutaneous electrode entry route and the epidural space. In the other two patients a breakage in the connection between the electrode’s point-of-exit from the skin and the external impulse generator caused us to discontinue treatment. Both complications occurred only in patients in whom the external impulse generator was used; in patients in whom the subcutaneous impulse generator was applied, there was no complication. The external impulse generator is designed to be used only during the neurostimulation trial period (3–6 weeks), and the connection break described occurred in approximately the 4th to 6th week after electrode insertion. Standard radiotherapy requires approximately 6 weeks plus time for the postsurgery period and for simulation and planning of radiotherapy.

The high percentage of infections that occurred in our study compared with the 2% rate demonstrated in other series7 could be explained by the immunodepression that is common in patients with cancer and the frequent use of corticosteroid agents in patients with brain tumors. In hindsight, we think that it may be preferable to use a subcutaneous impulse generator in future studies of SCS in patients with cancer so that these complications can be minimized. Even so, during the period of neurostimulation in our study, patients experienced no side effects other than an occasional upper limb paresthesia. Indeed, some patients reported a feeling of well-being while the SCS system was switched on.

The effects of cervical SCS are quite selective and appear to be most effective in the brain, head and neck, and upper limbs. Spinal cord stimulation has a segmental vascular effect, depending on the part of the spinal cord receiving the stimulus, and therefore exhibits fewer systemic effects than those associated with the use of vasoactive drugs. As such, a systemic vasodilation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phentoin interaction as has occurred with other hypoxia modifiers such as nicotinamide.41,46,55 Spinal cord stimulation is a reversible stimulus, and therefore exhibits fewer systemic effects than those associated with the use of vasoactive drugs. As such, a systemic vasodilation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phentoin interaction as has occurred with other hypoxia modifiers such as nicotinamide.41,46,55 Spinal cord stimulation is a reversible stimulus, and therefore exhibits fewer systemic effects than those associated with the use of vasoactive drugs. As such, a systemic vasodilation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phentoin interaction as has occurred with other hypoxia modifiers such as nicotinamide.41,46,55 Spinal cord stimulation is a reversible stimulus, and therefore exhibits fewer systemic effects than those associated with the use of vasoactive drugs. As such, a systemic vasodilation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phentoin interaction as has occurred with other hypoxia modifiers such as nicotinamide.41,46,55 Spinal cord stimulation is a reversible stimulus, and therefore exhibits fewer systemic effects than those associated with the use of vasoactive drugs. As such, a systemic vasodilation with the associated potential decrease in blood pressure is circumvented. Similarly, SCS is not associated with gastrointestinal toxicity or phentoin interaction as has occurred with other hypoxia modifiers such as nicotinamide.41,46,55
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Conclusions
Ischemia and hypoxia in high-grade malignant brain tumors may limit treatment efficacy. The results of this study indicate that, in patients with brain tumors, cervical SCS can increase blood flow in the CCA and the MCA as well as tumor perfusion, as assessed on SPECT studies. This increase in locoregional blood flow could lead to increased locoregional delivery of O₂, radiosensitizing agents, and chemotherapeutic drugs. The potential usefulness of SCS as an adjuvant in these locally aggressive tumors merits further investigation.

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Dr. Robaina is a consultant for Medtronic Ibérica (Madrid, Spain).

References


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