Volume 20, Number 4, April 1989

Spinal Cord Blood Flow and Systemic Blood Pressure After Experimental Spinal Cord Injury in Rats

Abhijit Guha, MD, Charles H. Tator, MD, PhD, FRCS(C), and James Rochon, PhD

We looked at the relation between systemic arterial blood pressure and recovery from spinal cord injury by inducing both hypertension and hypotension in 25 rats randomly allocated to five equal groups. The rats received no injury, a mild (2.3-g), or a severe (53.0-g) spinal cord injury lasting 1 minute. We used the hydrogen clearance technique to measure spinal cord blood flow at the injury site (T1) and at an adjacent site (C6). Mean systemic arterial blood pressure was either increased with adrenaline or decreased by phlebotomy in 20-mm-Hg intervals except for the severe-injury group, in which the posttraumatic pressure could only be increased with adrenaline. Spinal cord blood flow remained constant in the no-injury group between 81 and 180 mm Hg. After a mild injury, induced moderate hypertension (121-140 mm Hg) improved spinal cord blood flow significantly, whereas hypotension decreased it in a linear fashion. Severe injury caused a marked decrease in spinal cord blood flow and mean systemic arterial blood pressure. Even extreme hypertension (161-180 mm Hg) induced by adrenaline did not significantly increase spinal cord blood flow at T1 but caused hyperemia at C6 due to loss of autoregulation. In conclusion, normotension should be attempted, irrespective of the severity of spinal cord injury. Induced hypertension after severe spinal cord injury was not beneficial in improving spinal cord blood flow at the injury site while potentially increasing hemorrhage and edema. (Stroke 1989;20:372-377)

Cerebrovascular autoregulation, a means of maintaining stable cerebral blood flow (CBF) over a wide range of mean systemic arterial blood pressures (MSAPs), is affected by many lesions including trauma, ischemia, and tumors. There are numerous similarities between the spinal and the intracranial vasculatures, including autoregulation, but there has been minimal study of the effect of spinal cord injury (SCI) on autoregulation in the cord.

SCI causes local and systemic effects. Locally, its acute effects include hemorrhagic necrosis of the cord, mainly of the gray matter. Subsequently, posttraumatic ischemia and infarction may extend the damage throughout the full cross section of the cord, with a considerable longitudinal spread of ischemia. Systemically, SCI (especially in the cervical region) causes hypotension, due not just to interruption of sympathetic fibers but also to direct myocardial dysfunction. Moreover, these local and systemic alterations are not mutually exclusive since systemic hypotension can potentiate the damage due to local posttraumatic ischemia. Similarly, induced systemic hypertension may increase the amount of hemorrhagic necrosis. Thus, the relations between MSAP and spinal cord blood flow (SCBF) are of crucial importance for the management of patients with SCI. We examine these relations in an experimental model of acute SCI in rats.

Materials and Methods

We anesthetized male Wistar rats weighing 400-500 g (Charles River [Canada] Inc., St. Constant, Canada) with an intraperitoneal injection of chloralose and urethane (1:7). We cannulated both femoral arteries and both femoral veins with Intramedic PE-50 polyethylene tubing (Clay Adams Ltd., Persippany, New Jersey). MSAP in the left femoral artery was monitored with a multichannel transducer (recorder No. 7758A, Hewlett Packard [Canada] Ltd., Mississauga, Canada). The right femoral artery was cannulated for arterial blood gas (ABG) and hematocrit (Hct) sampling and phlebotomy in the designated rats. The left femoral vein was...
Rats were randomized to five groups after two preinjury measurements. Body temperature (Tb) was monitored with a rectal thermoprobe (Yellow Springs Instrument Co., Yellow Springs, Ohio). After a midline tracheostomy, 0.7 mg pancuronium bromide was given intravenously every 30 minutes and the rats were ventilated using a No. 680 rodent respirator (Harvard Bioscience, South Natick, Massachusetts). PaO₂ was maintained at 100–140 mm Hg with a 1:1 N₂O/O₂ mixture, and changes were made in the ventilator settings according to ABG.

We used the hydrogen clearance technique to measure SCBF at the injury site (T1) and an adjacent segment (C6). Under microscopy and with the dura opened, we used a Narishige MTS micromanipulator (Medical Systems Corp., Great Neck, New York) to insert platinum/iridium electrodes (Medwire Corp., Vermont) to a depth of 500 μm, one at C6 and two straddling the midline dorsal vein at T1. A 30-minute stabilization period was then allowed before recording of SCBF. At the onset of SCBF recording, 5–7% hydrogen was administered for 10 minutes through the ventilator; during a 20-minute desaturation phase the hydrogen clearance curve was recorded. The output of the electrodes was digitized and subsequently analyzed by a Jade System 3 S-100 microcomputer (Rochester, New York). The initial slope index (ISI) calculated from the natural-log plot of the clearance curve between 3 and 11 minutes was used to compute SCBF. Each measurement included SCBF at T1 and C6 and the average of the two T1 recordings, MSAP, ABG, Hct, and Tb (Figure 1).

Following the second preinjury measurement, the electrodes were removed and the 25 rats were randomized into five equal groups. We used the clip compression injury model to deliver a 2.3-g (mild) or a 33.0-g (severe) SCI for 1 minute to T1 after a C5 to T2 laminectomy. Groups 1 and 2 did not receive a SCI but had MSAP increased or decreased, respectively; Groups 3 and 4 received a mild SCI and had MSAP increased or decreased, respectively; Group 5 received a severe SCI and had MSAP increased as it was impossible to decrease MSAP further because of profound posttraumatic hypotension.

The electrodes were inserted again immediately after SCI, and the first postinjury measurements were made after a 30-minute stabilization period. MSAP was then increased by intravenous infusion of 1:10,000 adrenaline or decreased by phlebotomy in approximately 20-mm-Hg intervals between 20 and 180 mm Hg; measurements were made every 30 minutes. It was not always possible to achieve identical MSAP levels in all five rats in a group.

We calculated the means and standard errors of the mean (SEMs) for all parameters. We used analysis of variance (ANOVA) to determine the significance of differences in preinjury SCBF at T1 and C6, MSAP, ABG, Hct, and Tb among the five groups. The first postinjury measurements were combined into groups by injury severity: normal (Groups 1 and 2), mild SCI (Groups 3 and 4), and severe SCI (Group 5). We used ANOVA to determine the relations between SCI severity, postinjury SCBF at T1 and C6, and MSAP. Because MSAP in all five rats within a group was not exactly the same during each measurement, we stratified the data into 20-mm-Hg intervals and mean SCBF therefore represents the group’s average for a 20-mm-Hg interval of MSAP. We plotted the data for MSAP from 21 to 180 mm Hg, and we analyzed the differences between SCBF values using ANOVA for each MSAP interval. We used polynomial regression analysis of the relation between SCBF at T1 and C6 and MSAP for the severe SCI class. Over the range of MSAP examined, the normal or mild SCI comprised two groups each and thus could not undergo polynomial regression analysis.

**Results**

Preinjury MSAP was similar in all groups (Table 1). SCBF at C6 was consistently higher than that at T1 (Table 1). Preinjury pH, PaCO₂, Hct, and Tb were also similar in all five groups (Table 1) except for PaCO₂ in Group 2, which was significantly (p<0.05) lower.

MSAP decreased linearly with increasing SCI; for the mild SCI class MSAP was 88±17 mm Hg for the severe SCI class it was 14.4±4.4 and 26.2±4.6 ml/100 g/min and for the severe SCI class it was 14.4±4.4 and 26.2±4.6 ml/100 g/min at T1 and C6, respectively.

The normal class showed minimal change in SCBF at C6 with increasing MSAP (Figure 3, left) from 81–100 to 181–200 mm Hg. However, below the lower limit of autoregulation, SCBF at C6 decreased markedly with further hypotension (Group 2). After SCI but before manipulation of MSAP, mild SCI caused MSAP to decrease to 81–100 mm Hg, with a SCBF at C6 of 43.3±11.3 ml/100 g/min
TABLE 1. Physiologic Parameters in Rats Before Spinal Cord Injury

<table>
<thead>
<tr>
<th>Groups</th>
<th>MSAP (mm Hg)</th>
<th>SCBF (ml/100 g/min)</th>
<th>pH</th>
<th>PaCO2 (mm Hg)</th>
<th>Hct (%)</th>
<th>Tb (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103±6</td>
<td>54.3±4.5</td>
<td>66.5±5.5</td>
<td>7.36±0.01</td>
<td>39.9±1.5</td>
<td>52±2</td>
</tr>
<tr>
<td>2</td>
<td>110±6</td>
<td>60.3±4.5</td>
<td>64.0±5.5</td>
<td>7.39±0.01</td>
<td>32.8±1.5*</td>
<td>49±2</td>
</tr>
<tr>
<td>3</td>
<td>112±6</td>
<td>57.0±4.5</td>
<td>61.5±5.5</td>
<td>7.35±0.01</td>
<td>35.9±1.5</td>
<td>47±2</td>
</tr>
<tr>
<td>4</td>
<td>110±6</td>
<td>55.8±4.5</td>
<td>66.9±5.5</td>
<td>7.36±0.01</td>
<td>36.9±1.5</td>
<td>51±2</td>
</tr>
<tr>
<td>5</td>
<td>113±6</td>
<td>54.5±4.5</td>
<td>64.4±5.5</td>
<td>7.35±0.01</td>
<td>35.9±1.5</td>
<td>54±2</td>
</tr>
</tbody>
</table>

*Data are mean±SEM. MSAP, mean systemic arterial blood pressure; SCBF, spinal cord blood flow at injury (T1) and adjacent (C6) sites; SCBF at C6 was higher than that at T1 due to cervical enlargement; Hct, hematocrit; Tb, body temperature.

*p<0.05, different by analysis of variance.

In the normal class, SCBF at T1 did not change as MSAP rose above 81-100 mm Hg (Group 1); below this level SCBF at T1 decreased with MSAP (Group 2; Figure 3, left). Mild SCI decreased SCBF at T1 (28.4±5.2 and 26.4±7.0 ml/100 g/min in Groups 4 and 3, respectively; Figure 3, right). Decreasing MSAP (Group 4) caused further posttraumatic ischemia; restoration of normotension (101-120 mm Hg) or moderate hypertension (121-140 mm Hg) in Group 3 significantly improved SCBF at T1 to 40.5±5.6 and 42.8±6.8 ml/100 g/min, respectively. In the severe SCI class, polynomial regression analysis demonstrated a linear relation between SCBF and MSAP, with a very low slope of 0.32 ml/100 g/min/mm Hg (Figure 3, bottom). SCBF improved from 16.2±4.4 to 25.9±8.0 ml/100 g/min with normotension (101-120 mm Hg), but extreme hypertension (161-180 mm Hg) failed to increase SCBF further at T1.

Discussion

The autoregulatory ability of the intracranial circulation was established by the initial observations of Fog.1,2 The spinal and intracranial microcirculations are similar, including their ability for autoregulation.20-24 As we also confirmed, Flohr et al20 demonstrated both spinal cord autoregulation and CO2 reactivity in cats. Paleske24 using the heat clearance technique in pigs and Kindt 21 using the Peltier flow devices in monkeys showed similar findings. Spinal cord autoregulation was quantitatively shown by Kobrine et al22 and others23-25 using different methods of SCBF measurement. The mechanism of autoregulation is unknown.4 The spinal cord, if isolated from descending modulation, is able to autoregulate, suggesting a myogenic or local metabolic mechanism.26 Kobrine et al27,28 and Young et al29 proposed involvement of SCBF regulation by the sympathetic nervous system; however, the role of catecholamines in modulating SCBF in the normal or injured state is controversial.7,11,17

Preinjury SCBF and MSAP were similar for all groups (Table 1). SCBF values were similar to those we found previously in rats with either the hydrogen clearance technique or [14C]antipyrine autoradiography.6,11,13,29 The higher SCBF at C6 corresponds to the cervical enlargement. Groups 1 and 2 showed autoregulation with a lower limit of approximately 80 mm Hg, which is slightly higher than that recorded by other investigators, probably due to differences in species and SCBF techniques.21-23,26
Guha et al Spinal Cord Blood Flow After Injury 375

We could not demonstrate the upper limit of autoregulation, even with a MSAP of 180 mm Hg. Hypertension induced by agents such as adrenaline, noradrenaline, or angiotensin is artificial but unavoidable. Intracarotid injection of these agents showed no direct effect on CBF; thus, changes in CBF or SCBF should be secondary to changes in MSAP. Our failure to break the upper limit of autoregulation suggests that adrenaline at high doses may cause direct vasoconstriction of the spinal vessels, preventing an increase in SCBF.

SCI caused a dose-dependent decline in SCBF at both T1 and C6; the mild SCI class had a 45% decline in SCBF (from 56.4±4.5 to 29.8±5.3 ml/100 g/min) and the severe SCI class a 70% decrease (54.5±4.5 to 16.2±4.4 ml/100 g/min) at T1. Griffiths et al using a 300- or 500-g×cm weight-drop SCI model in the canine cord found 30% and 60% declines in SCBF, respectively. Ducker et al documented no decrease and a 66% decrease in SCBF in paraparetic and paraplegic monkeys, respectively. Kato et al noted a progressive decline in SCBF with increasing compression due to expanding epidural tumors until a critical level, above which there was an accelerated deterioration in both SCBF and neurologic function.
Our previous studies with mild SCI indicated minimal loss of function, even though SCBF decreased by 45%22 (normal 80°, 2.3 g 65°, 53.0 g 34° after 15 minutes of compression). This suggests that the postinjury SCBF at T1 after mild SCI did not cause total infarction of the spinal cord. The threshold of SCBF for electrical activity and cellular viability has not been determined. Hitchon et al33 demonstrated persistent autoregulation at 40 mm Hg with intact somatosensory evoked potentials in noninjured lambs. Kobrine et al34 concluded that spinal conduction was more resistant to ischemia than cortical responses and was lost only after an 8–18-minute period of essentially no SCBF.

Posttraumatic ischemia persisted and worsened with hypotension. MSAP was below the lower limit of autoregulation (Figure 3, right) after a mild SCI, with large decreases in SCBF with small changes in MSAP. Griffiths et al33 also observed that hypotension after mild SCI decreased SCBF and electrical conduction. Hypotension after SCI depended on severity of the injury. Aside from the effects of sympathectomy due to cervical SCI, myocardial dysfunction and cardiac arrhythmias35 may play a significant role in hypotension. Correction therefore may require intravascular fluid replacement, antiarrhythmic agents, inotropic agents, or invasive cardiac monitoring such as with a Swan-Ganz catheter.16,36,37

The SCBF–MSAP relation after SCI was examined by Senter and Venes1 in cats after a severe (500-g×cm) SCI. SCBF and autoregulation were maintained for 60–90 minutes after SCI, followed by deterioration of both. Collmann et al8 demonstrated a more immediate loss of autoregulation and CO2 reactivity in dogs after SCI. We demonstrated autoregulation in the normal and mild SCI classes, although two main differences existed (Figure 3, left and right; Figure 4). First, the curve for the mild SCI class plateaued at a MSAP lower than that of the normal class; second, the lower limit of autoregulation was higher in the mild SCI class (101–120 mm Hg) than in the normal class (81–100 mm Hg). At a MSAP of <100 mm Hg, SCBF at T1 was identical for both the mild and severe SCI classes as autoregulation was lost at the lower range of MSAP. Restoration of normotension (101–120 mm Hg) improved SCBF at both T1 and C6 in the mild SCI class. Moderate hypertension (121–140 mm Hg) would place the mild SCI class further along the plateau phase and prevent a precipitous drop in SCBF if there were a small decline in MSAP. Furthermore, at C6 with intact autoregulation, a risk of causing massive hyperemia was absent.

The SCBF–MSAP relation in the severe SCI class was different (Figure 3, bottom; Figure 4). Autoregulation was lost after severe SCI as shown by the linearity of the graphs. Hypertension would produce only a small gain in SCBF at T1 due to the very gradual slope of the SCBF vs. MSAP curve. For example, SCBF doubled from 14.4±3.3 to 31.3±3.5 ml/100 g/min as MSAP rose from 50 to 180 mm Hg.

The extreme hypertension (180 mm Hg) in achieving this, however, may be deleterious due to hyperemia at C6 as the SCBF–MSAP relation had a much steeper slope; at 180 mm Hg SCBF at C6 was 85.5±19.4 ml/100 g/min, higher than normal (Figure 3, left).

Therefore, restoration of normotension should be a major goal in the early management of SCI, irrespective of severity. However, extreme hypertension would not significantly improve SCBF further at T1 and may cause undesirable hyperemia with increased edema or hemorrhage at C6, especially after severe SCI. Other treatment modalities elevating posttraumatic SCBF by acting preferentially and directly on the spinal microvasculature without requiring hypertension would theoretically be advantageous. We have shown that nimodipine, a calcium channel blocker, when combined with a vasopressor (adrenaline) to maintain normotension, produced significant improvement in posttraumatic SCBF11,38 with no increase in the amount of hemorrhage. Theoretically, a combination of these therapeutic maneuvers may improve neurologic recovery after SCI by helping to restore SCBF.

In conclusion, we systematically examined the crucial relation between MSAP and SCBF after mild and severe SCI. Systemic hypotension must be avoided or corrected after a SCI of any severity. Autoregulation was maintained after mild SCI, with the lower limit set to a higher MSAP; thus, moderate hypertension was useful in mildly injured rats. Restoration of normotension was beneficial after severe SCI. However, hypertension did not increase SCBF and could potentially increase hemorrhage.
and edema at adjacent segments due to complete loss of autoregulation.

Acknowledgments

The authors are grateful to Mrs. L. Marmash, Mr. I. Piper, BSc, Miss Maria Vespa, and Miss Carolyn Dickson for their assistance.

References

1. Fog M: Cerebral circulation II. Reaction of pial arteries to increase in blood pressure. Arch Neurol Psychiatr 1939; 41:260–268

Key Words • blood pressure • cerebral ischemia • spinal cord • autoregulation
Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats.
A Guha, C H Tator and J Rochon

Stroke. 1989;20:372-377
doi: 10.1161/01.STR.20.3.372
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/20/3/372

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/