Regulation of Total and Regional Spinal Cord Blood Flow

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SUMMARY Studies of the regulation of total spinal cord blood flow have been limited by methodology. Total flow has been difficult to measure and flow to the gray and white matter within the cord has not been previously assessed. We have used labeled microspheres to measure blood flow in the spinal cord. Our purpose was to examine the effects of several physiological stimuli on the regulation of blood flow to different regions of the spinal cord (cervical, thoracic, and lumbosacral) and to different tissue in the cord (gray and white matter). The four types of stimuli examined were: chemical stimulation (alterations in systemic blood gases); autoregulation (increases in systemic pressure); neurogenic stimulation (activation of chemo- and baroreceptor reflexes); and metabolic stimulation (activation of spinal cord neurons). Studies were performed in dogs, sheep, and lambs; cerebral flow and spinal cord flow were measured simultaneously. Mean blood flow to the cervical and lumbosacral cord segments was 40% higher than flow to the thoracic cord. Under control conditions gray and white matter flows to the lumbosacral cord were 110 ± 15 (mean ± SE) and 25 ± 6 ml/min per 100 g, respectively. Chemical stimulation markedly altered spinal cord blood flow (hypoxia and hypercapnia increased flow; hypocapnia decreased flow), and distribution of flow to gray and white matter was unchanged. Autoregulation maintained total and regional spinal cord flow constant during increases in systemic pressure. Neurologic stimulation did not alter the tone of spinal cord blood vessels. Metabolic stimulation selectively increased blood flow to gray matter of the stimulated region. Regulation of total and regional spinal cord blood flow generally parallels that of the brain; chemical, autoregulatory, and metabolic factors are important determinants in the control of spinal cord blood flow.

PREVIOUS studies of the regulation of spinal cord blood flow have been limited by methodological problems.1-9 The anatomy of the arterial and venous system of the spinal cord precludes the use of standard techniques (arterial flow meters or venous collections) to measure spinal cord blood flow. Therefore, investigators have used clearance techniques or diffusable indicators to estimate spinal cord blood flow. These techniques have one or more of the following limitations: they (1) require invasion of the spinal canal; (2) permit only a single determination of blood flow; or (3) do not allow measurement of flow to the gray and white matter within the cord.

Recently we have suggested that 15-μm labeled microspheres can be used to accurately measure total and regional flow in the brain.10 We have now applied this method to study the regulation of total and regional spinal cord blood flow. Four physiological stimuli that could potentially affect spinal cord blood flow were examined. They are: (1) chemical stimulation (alterations in systemic blood gases); (2) autoregulation (increases in systemic pressure); (3) neurogenic stimulation (activation of chemo- and baroreceptor reflexes); and (4) metabolic stimulation (activation of spinal cord neurons). In these studies we wished to determine whether total and regional spinal cord blood flow was controlled by factors similar to those that regulate total and regional cerebral blood flow.

Methods

EXPERIMENTAL ANIMALS

Thirty-three mongrel dogs weighing 16-30 kg were anesthetized with chloralose (50 mg/kg) and urethane (500 mg/kg), iv. Five sheep weighing 50-55 kg and seven lambs weighing 7-20 kg required a smaller dose of anesthesia (chloralose, 25 mg/kg; urethane, 250 mg/kg), iv. The dogs were treated with decamethonium bromide (0.3 mg/kg, iv) and all animals were treated with heparin (500 U/kg, iv) and ventilated artificially via a cuffed endotracheal tube with air and supplemental O₂.

Our initial studies were performed in dogs. However, in these animals, the spinal cord contains relatively little gray matter and the gray matter could not be separated by dissection. To obtain measurements of flow to the gray and white matter within the cord, additional studies were done in sheep and lambs. In the lumbosacral cord of sheep and lambs, the gray matter is present in sufficient quantity so that gray and white matter can be separated by dissection. In experiments performed in the spring lambs were used because removal of the spinal cord is easier in lambs than in sheep.

HEMODYNAMICS AND BLOOD GASES

Arterial pressure was measured with a Statham P23Db strain gauge leveled at the midchest position. The pressure
signal was recorded on a direct-writing recorder. Arterial P O2, P CO2, and pH were measured with an Instrumentation Laboratory Ultramicro-gas analyzer.

**MEASUREMENT OF SPINAL CORD BLOOD FLOW**

The heart was exposed via a left thoracotomy and a cannula was placed in the left atrium for injection of microspheres. Two cannulas were placed in arteries for withdrawal of reference blood samples. In studies in which the distal aorta was occluded (see below), the reference blood samples were obtained from arteries cephalad to the site of aortic occlusion. Microspheres with a mean diameter of 15 μm were injected into the left atrium. Injection of microspheres labeled with 141Ce, 85Sr, 46Sc, 125I, and 51Cr allowed us to make five measurements of spinal cord blood flow. The order in which the isotopes were injected was varied. The method of microsphere preparation and injection, and withdrawal of reference arterial blood samples, was identical to that previously reported from our laboratory.15 The number of microspheres used in each injection varied between 1.6 and 12.2 x 106 spheres. At the end of each study the animal was killed and segments of the spinal cord and the entire brain were excised. In studies that involved neurogenic stimulation, samples of the nonperfused gracilis muscle and small bowel also were excised. In the studies that involved the effects of chemical stimulation and autoregulation on spinal cord blood flow in dogs, the entire spinal cord from C1 to the cauda equina was excised. The cord was divided into cervical, thoracic, and lumbar sacral segments using anatomical landmarks. Segments of white matter from these regions were separated so that white matter flow could be compared to total cord flow. In the studies that involved the effects of reflex stimulation on cord flow, only total flow to the cervical spinal cord from C1 to C7 was examined. In studies of the effects of chemical stimulation, autoregulation, and metabolic stimulation on spinal cord blood flow in sheep and lambs, blood flow was measured in segments of the cervical cord (C1 to C5), thoracic cord (T9 to T13), and the lumbar sacral cord (L1 to the cauda equina). The lumbar sacral cord was bisected (left and right) and the gray and white matter were separated by dissection. The brain was cut into multiple small sections weighing between 0.2 and 4 g. Cerebral white matter consisted of pooled samples of corpus callosum, centrum ovale, and optic chiasm; cerebral gray matter consisted of pooled samples of caudate nucleus and cortical gray. The medulla was separated from the pons and cervical cord by use of anatomical landmarks. Blood flows were reported as the weighted mean flow of the samples that comprise any given subdivision. Total brain flow is the weighted mean flow of the cerebrum, cerebellum, and brainstem.

The tissue samples were weighed, placed in glass tubes, and counted for 5 minutes in a 3-inch well-type gamma counter. The reference blood samples were divided into portions so that their counting geometry was similar to that of the tissue samples. The energy windows used were 46Sc, 700-1500 keV; 85Sr, 400-600 keV; 51Cr, 270-370 keV; 141Ce, 125-175 keV; and 125I, 20-50 keV. Isotope separation was performed according to standard techniques.11 The output of the gamma counter was punched on paper tape and processed on a PDP-11 computer. To calculate spinal cord blood flow we used the formula SCBF = Csc x 100 RBF/CR, where SCBF = spinal cord blood flow in ml/min per 100 g of spinal cord, Csc = counts/g of spinal cord tissue, RBF = reference blood flow (rate of withdrawal of blood samples from arteries), and CR = total counts in reference arterial blood. The counts in the two reference blood samples were averaged. Blood flow to brain, skeletal muscle, and small bowel were calculated similarly.

**CAROTID PERFUSION AND INJECTION**

The carotid bifurcations were exposed and the internal carotid and all branches of the external carotid artery were ligated. Arterial blood was pumped into one or both common carotid arteries. Carotid baroreceptors were stimulated by changes in carotid perfusion pressure made with a Starling resistor as previously described.12 To counterbalance the systemic vasodilation associated with baroreceptor stimulation, a cuff was placed around the thoracic aorta near the diaphragm. Inflation of the cuff occluded or obstructed the aorta and increased arterial pressure in the cephalad portion of the body by 25-70 mm Hg. During baroreceptor stimulation the cuff was inflated and consequently the blood pressure in the cephalad portion of the body remained relatively constant. In the studies in which the chemoreceptors were stimulated, the occipital artery was ligated 1-2 cm from its origin so that the blood supply of the carotid body was preserved. A small needle was inserted into the common carotid artery in these studies for infusion of nicotine.

**PERFUSION OF THE GRACILIS MUSCLE**

Vascular responses to baroreceptor or chemoreceptor stimulation were observed during each study in an isolated innervated perfused gracilis muscle.13 When the muscle is perfused at constant flow an increase in perfusion pressure indicates vasoconstriction and a decrease in pressure indicates vasodilation. The injection of microspheres for measurement of spinal cord blood flow during reflex neurogenic stimulation was made at the time that the maximal change in perfusion pressure of the gracilis artery occurred.

**NERVE STIMULATION**

The intact left sciatic and femoral nerves of lambs were isolated and stimulated electrically. The stimulator (Grass Medical Instruments, model 59B) delivered 4-msec square wave pulses at 30 V and a frequency of 5 Hz.

**INNERVATION OF SPINAL CORD VESSELS**

In three dogs, the catecholamine content of the anterior spinal artery of the cervical cord and the cerebral vessels which constitute the circle of Willis was measured by methods previously described.13,14 In addition, histofluorescence studies using the technique of Falck and Hillarp were made to visualize the location of catecholamines in these vessels.15
PROCEDURES

Effects of Chemical Stimulation and Autoregulation

The effects of chemical stimulation (systemic hypercapnia, hypocapnia, and hypoxia [in sheep only]) and autoregulation (increases in systemic pressure) on total and regional spinal cord blood flow were examined in four dogs and five sheep. The order of these interventions was varied.

Alterations in blood gases were achieved by either altering the inhaled gas mixture or respiratory minute volume. Thus, hypercapnia was produced by adding 10% CO₂ and 90% N₂ (2-3 liters/min) to the inhaled gas; hypocapnia and hypoxia by changing inhaled gas to a mixture of 10% CO₂ and 90% N₂ (2-3 liters/min) and 8% O₂ and 92% N₂ (1-2 liters/min); hypoxia by changing the inhaled gas to 8% O₂ and 92% N₂ (1-2 liters/min); and hypocapnia by increasing respiratory rate and volume. Whenever blood gases were altered, they were maintained at the new level for at least 15 minutes before spinal cord blood flow was measured.

Phenylephrine (500 μg/min, iv) was used to increase systemic pressure. This drug does not cross the blood-brain barrier and presumably has no direct effect on vessels within the central nervous system. Whenever pressure was increased with phenylephrine, the increase was maintained for at least 3-5 minutes before flow measurements were obtained.

Effects of Reflex Neurogenic Stimulation

The effects of chemoreceptor stimulation on cervical cord blood flow was examined in 12 dogs. Cervical cord blood flow was measured under control conditions and during an intracarotid infusion of nicotine bitartrate (20-100 μg/min) for 1-3 minutes. In six of the 12 dogs cervical spinal blood flow was measured during another control period and during systemic hypercapnia and hypoxia. The latter measurement was made to demonstrate that cervical cord blood vessels were responsive to a vasodilator stimulus. Mean arterial pressure during control was 95 ± 14.1 mm Hg and did not vary significantly during the three interventions. Blood gases and pH were arterial PO₂ = 109 ± 5.8 mm Hg, arterial PCO₂ = 38 ± 0.4 mm Hg, and pH = 7.39 ± 0.01 during control. These values did not vary significantly during nicotine injection or during the second control period. During hypercapnia, blood gases and pH were arterial PO₂ = 71 ± 7.1 mm Hg, arterial PCO₂ = 61 ± 1.8 mm Hg, and pH = 7.26 ± 0.02.

The effects of baroreceptor stimulation on cervical spinal cord blood flow were examined in 14 dogs. Cervical cord blood flow was measured under control conditions (carotid perfusion pressure = 100 ± 3 mm Hg) and after increasing perfusion pressure in the isolated carotid sinus to 199 ± 1 mm Hg for 1-4 minutes to stimulate carotid baroreceptors. The injection of microspheres during baroreceptor stimulation was made at the time that the decrease in gracilis perfusion pressure was maximal. In 10 of these dogs cervical cord blood flow was measured during a second control period and during hypocapnia. The latter measurement was made to demonstrate that the cervical cord blood vessels were responsive to a vasoconstrictor stimulus. Mean arterial pressure in the cephalad part of the body during control was 103 ± 4 mm Hg and did not vary significantly during the experiment. Blood gases and pH during control were arterial PO₂ = 39 ± 0.4 mm Hg, arterial PO₂ = 126 ± 5.0 mm Hg, and pH = 7.37 ± 0.003. No significant changes occurred during baroreceptor stimulation or the second control period. During hypocapnia, blood gases and pH were as follows: arterial PO₂ = 22 ± 0.8 mm Hg, arterial PO₂ = 123 ± 9 mm Hg, and pH = 7.47 ± 0.01.

Effects of Metabolic Stimulation

The effects of a metabolic stimulus on regional lumbar-sacral cord blood flow was examined in seven lambs. Lumbar-sacral cord blood flow was first measured under control conditions and then during electrical stimulation of the intact femoral and sciatic nerves. Nerve stimulation was accompanied by visible contractions of the musculature in the left lower limb. Thus, input to the lumbar-sacral cord neurons could potentially arrive antegrade via somatic afferent fibers (either from direct electrical stimulation or indirect stimulation originating from proprioceptive receptors in muscle) and retrograde via efferent fibers. Flow measurements were made during the last 5 minutes of a 10-minute period of nerve stimulation.

STATISTICAL ANALYSIS

Statistical analysis was performed with either a t-test for paired or unpaired data or, when more than two values were compared, an analysis of variance. Data are expressed as the mean ± 1 SE.

Results

TOTAL AND REGIONAL SPINAL CORD BLOOD FLOW DURING CONTROL CONDITIONS

Under control conditions in both dogs and sheep, blood flow to the spinal cord (expressed per unit of weight) was about 40% of that to the brain (Tables 1 and 2). Furthermore, the thoracic cord blood flow was about 40% less than flow to the cervical or lumbo-sacral cord segments (Tables 1 and 2; Fig. 1). Flow to the gray matter in the lumbo-sacral cord in sheep was about 4-fold greater than white matter flow in the lumbo-sacral cord (Table 2 and Fig. 1). The lesser proportion of gray matter in the thoracic cord probably explains why thoracic cord blood flow tends to be somewhat lower than flow to the cervical and lumbo-sacral cord segments.

EFFECTS OF CHEMICAL STIMULATION ON SPINAL CORD BLOOD FLOW

Hypercapnia caused a marked increase in spinal cord blood flow and hypocapnia caused a marked decrease in spinal blood flow to all regions (cervical, thoracic, and lumbo-sacral) of the spinal cord in both dogs and sheep (Tables 1 and 2). In the gray and white matter of the lumbo-sacral cord of sheep, hypercapnia increased flow and hypocapnia decreased flow (Table 2). Hypoxia in sheep also markedly increased flow in all regions and tissues of the spinal cord (Table 2). Thus, chemical stimuli
TABLE 1  Regulation of Blood Flow to the Spinal Cord (Dogs)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Systemic hypertension</th>
<th>Hypocapnia</th>
<th>Hypercapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>110 ± 8</td>
<td>152 ± 8</td>
<td>88 ± 8</td>
<td>80 ± 18</td>
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<tr>
<td>Systemic blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>123 ± 12</td>
<td>135 ± 5</td>
<td>123 ± 1</td>
<td>123 ± 22</td>
</tr>
<tr>
<td>Arterial Pco2 (mm Hg)</td>
<td>39 ± 0.6</td>
<td>37 ± 1</td>
<td>24 ± 2.3</td>
<td>55 ± 2</td>
</tr>
<tr>
<td>pH</td>
<td>7.36 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.49 ± 0.03</td>
<td>7.16 ± 0.02</td>
</tr>
<tr>
<td>Spinal cord blood flow (ml/min per 100 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total spinal cord</td>
<td>32 ± 7.0</td>
<td>30 ± 5.1</td>
<td>18 ± 3.8</td>
<td>59 ± 14.04</td>
</tr>
<tr>
<td>Cervical cord</td>
<td>34 ± 7.7</td>
<td>32 ± 5.5</td>
<td>18 ± 4.1</td>
<td>59 ± 14.9</td>
</tr>
<tr>
<td>Cervical white matter</td>
<td>18 ± 8.8</td>
<td>22 ± 4.8</td>
<td>13 ± 4.7</td>
<td>35 ± 10.4</td>
</tr>
<tr>
<td>Thoracic cord</td>
<td>29 ± 6.4</td>
<td>27 ± 5.4</td>
<td>16 ± 2.9</td>
<td>49 ± 14.6</td>
</tr>
<tr>
<td>Thoracic white matter</td>
<td>20 ± 6.4</td>
<td>20 ± 4.6</td>
<td>12 ± 3.6</td>
<td>35 ± 12.5</td>
</tr>
<tr>
<td>Lumbar cord</td>
<td>34 ± 8.1</td>
<td>33 ± 5.8</td>
<td>23 ± 5.0</td>
<td>52 ± 19.7</td>
</tr>
<tr>
<td>Lumbar white matter</td>
<td>23 ± 6.8</td>
<td>22 ± 4.3</td>
<td>15 ± 6.0</td>
<td>52 ± 19.7</td>
</tr>
<tr>
<td>Cerebral blood flow (ml/min per 100 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total brain</td>
<td>75 ± 10.9‡</td>
<td>83 ± 8.9</td>
<td>30 ± 4.4†</td>
<td>174 ± 17.1**‡‡</td>
</tr>
<tr>
<td>Cortical gray</td>
<td>85 ± 19.3</td>
<td>105 ± 25.9</td>
<td>33 ± 3.5</td>
<td>209 ± 26.4**‡‡</td>
</tr>
<tr>
<td>Cortical white</td>
<td>40 ± 2.0</td>
<td>42 ± 2.0</td>
<td>18 ± 2.8*</td>
<td>63 ± 6.2**‡‡</td>
</tr>
<tr>
<td>Medulla</td>
<td>74 ± 12.2</td>
<td>72 ± 7.5</td>
<td>33 ± 5.3</td>
<td>199 ± 24.7**‡‡</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± 1 SE; n = 4.
* Significantly different from control at the 0.05 level of confidence.
† Significantly different from hypertension at the 0.05 level of confidence.
‡‡ Significantly different from hypocapnia at the 0.05 level of confidence.
§ The relatively high cerebral blood flow values in this group are probably related to the minimal surgical preparation required.

caused marked changes in the vascular resistance of spinal cord blood vessels but no redistribution of flow within the cord occurred.

EFFECTS OF SYSTEMIC HYPERTENSION ON SPINAL CORD BLOOD FLOW (AUTOREGULATION)

Increasing systemic pressure by 40–50 mm Hg did not alter flow to any region (cervical, thoracic, or lumbar sacral) of the spinal cord in either dogs or sheep (Tables 1 and 2). Furthermore, in sheep, flow to the gray and white matter of the lumbar sacral cord remained constant during increases in systemic pressure. This occurred because during systemic hypertension there was a marked increase in vascular resistance of the gray and white matter vessels (Table 2).

EFFECTS OF NEUROGENIC STIMULATION OF SPINAL CORD BLOOD FLOW

Studies of the catecholamine content of spinal cord blood vessels indicated that these vessels are richly innervated. The concentrations of catecholamines in the anterior spinal arterial was norepinephrine (NE), 4.4 ± 0.5 µg/g of tissue (wet weight). Cerebral vessels had NE concentrations of 5.7 ± 0.7 µg/g tissue (wet weight). Histofluorescence studies in these vessels showed a typical pattern of sympathetic innervation in the anterior spinal and cerebral vessels.

During chemostimulation, the integrity of the chemoreceptor reflex was tested by simultaneously measuring blood flow to the small bowel and the gracilis perfusion pressure. Chemoreceptor stimulation was associated with a decrease in small bowel flow (60.8 ± 7.7 to 39 ± 6.4 ml/min per 100 g) (P < 0.05) and an increase in gracilis perfusion pressure (136 ± 11.7 to 197 ± 10.9 mm Hg) (P < 0.01) which indicate that the chemoreceptor reflex was intact. During chemoreceptor stimulation with nicotine, cervical spinal cord flow did not change. Vasodilator responsiveness was preserved in the cervical cord as indicated by a marked increase in cervical spinal cord flow during hypercapnia (Fig. 2).

When pressure in the carotid bifurcation was raised, baroreceptors were activated as indicated by a decrease in heart rate (32 ± 5 beats/min) (P < 0.01), profound vasodilation of the nonperfused gracilis muscle (muscle blood flow increased from 3.2 ± 0.7 to 13.4 ± 2.6 ml/min per 100 g) (P < 0.01), and a marked decrease in gracilis perfusion pressure (124 ± 10 mm Hg to 87 ± mm Hg) (P < 0.01). Baroreceptor stimulation did not alter cervical spinal cord blood flow even though vasconstrictor responses of the cervical spinal cord vessels were intact, as indicated by vasoconstriction during hypocapnia (Fig. 3).

EFFECTS OF METABOLIC STIMULATION ON SPINAL CORD BLOOD FLOW

Under control conditions, arterial blood gases, pH, and mean systemic pressure were Po2 = 102 ± 8.7 mm Hg, Pco2 = 38 ± 1.6 mm Hg, pH = 7.51 ± 0.04, and XBP = 80 ± 6.4 mm Hg. These values did not change significantly during stimulation. Flow to the left and right gray matter was similar and flow to the left and right white matter was similar in the lumbar sacral spinal cord of lambs prior to nerve stimulation (Fig. 4). Stimulation of the intact left sciatic and femoral nerves (30 V, 5 Hz) resulted in a 50% increase in blood flow to the left gray matter of the lumbar sacral cord. Simultaneous measurement of flow to the ipsilateral white matter and to the contralateral white and gray matter of the lumbar sacral cord demonstrated that in these areas flow remained relatively stable (Fig. 4). In addition, flow to the thoracic spinal cord or
Table 2  Regulation of Blood Flow to Gray and White Matter of the Lumbosacral Spinal Cord (Sheep)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Hypertension</th>
<th>Hypocapnia</th>
<th>Hypercapnia</th>
<th>Hypoxia</th>
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<tr>
<td>Mean arterial/pressure (mm Hg)</td>
<td>75 ± 7.8</td>
<td>134 ± 8.0</td>
<td>74 ± 6.8</td>
<td>89 ± 5.4</td>
<td>71 ± 10.6</td>
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<td>Systemic blood gases</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>100 ± 9.5</td>
<td>101 ± 5.4</td>
<td>94 ± 9.2</td>
<td>105 ± 20.0</td>
<td>32 ± 4.3</td>
</tr>
<tr>
<td>Arterial Pco2 (mm Hg)</td>
<td>36 ± 0.5</td>
<td>39 ± 1.7</td>
<td>23 ± 1.7</td>
<td>56 ± 2.4</td>
<td>37 ± 1.6</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 ± 0.02</td>
<td>7.41 ± 0.01</td>
<td>7.61 ± 0.03</td>
<td>7.28 ± 0.02</td>
<td>7.42 ± 0.02</td>
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<td>Spinal cord blood flow (ml/min per 100 g)</td>
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<tr>
<td>Lumbosacral cord gray</td>
<td>32 ± 5.3</td>
<td>37 ± 5.5</td>
<td>15 ± 3.0</td>
<td>87 ± 17.0**†</td>
<td>53 ± 12.1</td>
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<tr>
<td>Lumbosacral cord white</td>
<td>23 ± 3</td>
<td>28 ± 3.4</td>
<td>9 ± 1.2</td>
<td>69 ± 12.6**†</td>
<td>42 ± 14.0</td>
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<td>Thoracic cord</td>
<td>30 ± 5.0</td>
<td>33 ± 4.4</td>
<td>13 ± 2.1</td>
<td>81 ± 14**‡</td>
<td>59 ± 15.3‡</td>
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<td>Cervical cord</td>
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</tr>
<tr>
<td>Regional lumbosacral cord blood flow (ml/min per 100 g)</td>
<td>110 ± 15.3</td>
<td>120 ± 22.2</td>
<td>57 ± 12.7</td>
<td>282 ± 70.2**‡</td>
<td>179 ± 40.1</td>
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<tr>
<td>Lumbosacral gray matter</td>
<td>25 ± 5.7</td>
<td>27 ± 7.3</td>
<td>14 ± 2.9</td>
<td>83 ± 16.1**‡</td>
<td>49 ± 16.6</td>
</tr>
<tr>
<td>Lumbosacral white matter</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Regional lumbosacral spinal cord vascular resistance [mm Hg/(ml/min per 100 g)]</td>
<td>0.7 ± 0.1</td>
<td>1.3 ± 0.2</td>
<td>1.6 ± 0.3*§¶</td>
<td>0.4 ± 0.06†</td>
<td>0.4 ± 0.03†</td>
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<tr>
<td>Lumbosacral gray matter</td>
<td>3.6 ± 0.9</td>
<td>6.6 ± 1.3*</td>
<td>6.4 ± 1.1§¶</td>
<td>1.2 ± 0.2†</td>
<td>2.1 ± 0.6†</td>
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<tr>
<td>Lumbosacral white matter</td>
<td>60 ± 3.6</td>
<td>69 ± 4.2</td>
<td>28.7 ± 1.9**‡</td>
<td>203 ± 10.5</td>
<td>103 ± 18.3</td>
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<tr>
<td>Total brain blood flow (ml/min per 100 g)</td>
<td>1.3 ± 0.1</td>
<td>2.0 ± 0.2*</td>
<td>2.6 ± 0.3*‡¶</td>
<td>0.4 ± 0.02*†</td>
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<tr>
<td>Total brain vascular resistance [mm Hg/(ml/min per 100 g)]</td>
<td>54 ± 3.4</td>
<td>68 ± 6.7</td>
<td>29 ± 1.9</td>
<td>219 ± 15.7**‡</td>
<td>92 ± 15.8</td>
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<td>Regional cerebral blood flow (ml/min per 100 g)</td>
<td>29 ± 4.8</td>
<td>39 ± 6.7</td>
<td>17 ± 1.7</td>
<td>86 ± 12.1**‡</td>
<td>56 ± 9.6*</td>
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<tr>
<td>Cortical gray</td>
<td>65 ± 7.4</td>
<td>64 ± 6.1</td>
<td>25 ± 2.3</td>
<td>200 ± 17.9**‡</td>
<td>129 ± 27.2†</td>
</tr>
<tr>
<td>Cortical white</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Medulla</td>
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</tbody>
</table>

Values are expressed as mean ± 1 SE; n = 5.
* Significantly different from control at the 0.05 level of confidence.
† Significantly different from hypertension at the 0.05 level of confidence.
‡ Significantly different from hypocapnia at the 0.05 level of confidence.
§ Significantly different from hypercapnia at the 0.05 level of confidence.
H Significantly different from hypoxia at the 0.05 level of confidence.

Discussion

The present investigation provides quantitative data on the response of total and regional spinal cord blood flow to the major factors which are thought to modulate it. The data have been obtained by a method which permits repeated measurements of spinal cord blood flow without invasion of the spinal canal. Three concepts which have been proposed for brain blood flow can now be extended to the regulation of spinal cord blood flow. They are as follows:

1. Autoregulation maintains regional as well as total spinal cord blood flow constant during moderate alterations in system pressure.
2. Spinal cord blood vessels have extensive sympathetic innervation but appear to be unresponsive to reflex stimuli.
3. Blood flow to the spinal cord gray matter selectively increased in response to a metabolic stimulus.

Previous studies of the regulation of spinal cord blood flow have used methods which require invasion of the spinal canal (heat clearance, 133 Xe and hydrogen clearance) or cannot be used to obtain repeated measurements (diffusible indicators). When total spinal cord blood flow has been measured under control conditions with techniques which permit quantitative assessment (carbonized or albumin spheres or a diffusible indicator) the values obtained have been similar to those reported in...
this study. Gray and white matter spinal cord blood flow has been reported for only one animal and the values (63 and 14 ml/min per 100 g for gray and white matter, respectively) were similar to those reported in this study. The higher flows measured in the spinal cord gray matter probably reflect the greater metabolic requirements of this tissue and correlate with the increase in vascularity of the gray matter.

In the present study, alterations in systemic blood gases caused marked changes in spinal cord blood flow from C to the cauda equina. Hypocapnia decreased blood flow and hypercapnia and hypoxia increased spinal cord blood flow. This is in agreement with data obtained by other investigators. In addition, the present study has shown that hypocapnia, hypercapnia, and hypoxia do not significantly alter the distribution of blood flow within the spinal cord.

In a previous study we noted that autoregulation maintains regional as well as total cerebral blood flow. The present study extends the concept of regional autoregulation to the spinal cord. Thus, moderate changes in systemic pressure did not alter gray or white matter blood flow in the spinal cord.

It seemed important to determine whether spinal cord blood flow was influenced by reflex stimuli because spinal cord blood vessels are richly innervated and studied. The effects of reflex stimuli in cerebral blood vessels have yielded disparate results. Although carotid baro- and chemoreceptor reflexes were intact and spinal cord blood vessels were responsive to vasoconstrictor and vasodilator stimuli, our studies demonstrated that carotid baroreceptor and chemoreceptor stimulation did not significantly alter spinal cord blood flow. We have recently reported that cerebral vessels are unresponsive to reflex stimuli. Thus, the present study suggests that spinal cord blood vessels are unresponsive to reflex neurogenic stimuli and supports the concept that blood vessels within the central nervous system are relatively unresponsive to reflex stimuli.

Several investigations have suggested that activation of groups of neurons within the brain is associated with an increase in regional metabolism and local cerebral vasodilation. It is now possible to extend this concept to the spinal cord because stimulation of spinal cord neurons was associated with a 50% selective increase in blood flow to the gray matter on the stimulated side. The electrical stimulation of the femoral and sciatic nerves presumably increased metabolism in the gray matter of the stimulated side. This presumption is supported strongly by a recent study which demonstrated that stimulation of femoral and sciatic nerves increases the rate of glucose metabolism in the gray matter of the spinal cord on the stimulated side.

Both clinical and experimental studies suggest that the gray matter of the spinal cord may be particularly vulnerable to ischemic injury. A syndrome of spinal cord claudication (DeJérine syndrome or pseudoclaudication) has been described in which patients develop progressive motor weakness and pain with walking which promptly disappears with rest. This might occur if blood flow to the spinal cord gray matter were relatively fixed by a pathological process and, as a result, it could not increase during neural activation. Under these conditions, ischemia of the gray matter of the local cord segments involved would occur and if sufficiently severe might interfere with neuronal function. Experimentally, when the thoracic aorta is ligated, the most profound histological alterations occur in the gray matter of the lumbo-sacral cord.

Furthermore, studies with 32P suggest that the blood-brain barrier is more severely altered in the gray matter in response to spinal cord ischemia. The relatively high blood flow requirements and the metabolic rate of the spinal cord gray matter, particularly during neural activity, provide an explanation for these clinical and experimental observations.

In summary, we have presented quantitative data on the response of total and regional spinal cord blood flow to several important factors which regulate it. Our data indicate the following: (1) chemical stimulation (achieved by changing systemic blood gases) alters total spinal cord blood flow but does not redistribute flow; (2) autoregulation of spinal cord blood flow extends to regional areas in the spinal cord; (3) spinal cord blood vessels are richly innervated but unresponsive to reflex stimuli; and (4) metabolic stimulation selectively increases flow to stimulated gray matter. Thus, it appears that in the spinal cord, chemical, autoregulatory, and metabolic factors predominate in the regulation of blood flow.

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References

Regulation of total and regional spinal cord blood flow.
M L Marcus, D D Heistad, J C Ehrhardt and F M Abboud

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