The effect of hypothermia on regional spinal cord blood flow in rats

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Spinal cord ischemia may accompany surgical procedures on the aorta or vertebral column. Regional spinal cord blood flow (SCBF) was measured at five vertebral levels in the spinal cords of pentobarbital-anesthetized rats based on the distribution of intravenously injected carbon-14-labeled butanol. In seven normal rats, mean SCBF (± standard error of the mean) ranged from 52.7 ± 5.4 to 68.5 ± 4.9 ml min⁻¹ . 100 gm⁻¹ (depending on the level, being lowest at the thoracic levels) and mean arterial blood pressure (MABP) was 126 mm Hg. Corporal hypothermia (mean rectal temperature 28.1° ± 0.6°C) was induced by cold exposure in seven other rats, and SCBF, measured immediately thereafter, was significantly elevated at all five levels by 52% to 69% compared to the normal group. However, MABP was elevated in the hypothermic group to 165 ± 4 mm Hg (p < 0.0001). Therefore, in seven additional hypothermic rats, MABP was maintained at the control level by withdrawal of arterial blood as necessary. In these animals, SCBF at all levels was still significantly elevated compared with the normal group and the values were nearly identical to those measured in the hypertensive hypothermic rats. It was concluded that hemodynamic autoregulation of SCBF is impaired in the presence of moderate systemic hypothermia in pentobarbital-anesthetized rats.

KEY WORDS • spinal cord blood flow • hypothermia • ¹⁴C-butanol • hemodynamic autoregulation • rat

S PINAL cord dysfunction may attend surgical procedures on the aorta or vertebral column. The pathogenesis of these indirect injuries, which typically result in motor deficits, is incompletely understood. There is considerable evidence, however, that decreased regional spinal cord blood flow (SCBF), below a critical range as yet undefined, is an important common factor.¹,¹⁰-¹₂,¹₆,²₄

Intraoperatively, systemic hypothermia has been used clinically in an effort to prevent postoperative cord dysfunction, especially when cross-clamping of the thoracic aorta is necessary.¹²,²³,²⁵ The underlying presumption is that ischemic injury may be minimized because of the decreased metabolic requirement of the cooled tissue.²,²¹ But hypothermic anesthesia is presently not widely used for this purpose, as the supportive clinical and experimental evidence is sparse, largely anecdotal, and in part conflicting. In this context, quantitation of the regional SCBF response to systemic cooling is clearly pertinent, if not essential. However, SCBF has not previously been measured in subjects with systemic hypothermia. The two studies that examined SCBF during local cooling presented conflicting data: in one, a qualitative "marked increase" in perfusion of profoundly cooled (13° to 16°C) feline spinal cord was observed;²⁷ in the other, topical cooling of the cord to a similar temperature resulted in a 50% decrease in the SCBF in the cooled segment in dogs.⁴

In the present investigations, the distribution of carbon-14 (¹⁴C)-labeled butanol (a method for the measurement of SCBF recently developed in this laboratory) was used to quantitate SCBF in anesthetized rats which had been made acutely hypothermic by exposure to an environmental temperature of 4°C. This protocol was approved by the Washington University School of Medicine Committee on the Humane Care of Laboratory Animals.

Materials and Methods

Animal Preparation

Twenty-one Sprague-Dawley rats, each weighing between 270 and 384 gm, were used for this study. They were anesthetized with 50 mg kg⁻¹ of pentobarbital following pretreatment with subcutaneous atropine 0.004 mg kg⁻¹. The fur over the neck and the midline of the posterior torso was clipped. Polyethylene cannulas were inserted in one external jugular vein and in both common carotid arteries through a short cervical incision. The tip of the right carotid cannula was posi-
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tioned just above the aortic valve and that of the left carotid cannula was placed at the aortic arch. Mean arterial blood pressure (MABP) was measured via the left carotid cannula with a transducer positioned at heart level and a pressure monitor.* Arterial blood pH, pO2, and pCO2 were determined using a pH/blood gas analyzer.† The blood gas data in hypothermic rats were corrected using a nomogram.6 A rectal probe was used to monitor body temperature, which was maintained near 37°C with an external infrared heat source in the control rats.

Flow measurements were performed with the rats in the prone position, precisely as described elsewhere.17-19 Briefly, a 0.1-ml bolus of 14C-butanol (25 µCi) was injected in less than 1 second through the venous catheter 5 seconds after a constant rate of arterial hemorrhage had been visually verified from the previously declamped left carotid catheter. Precisely 15 seconds after the indicator had been injected, 1.0 ml of cyanoacrylate glue was injected into the right carotid cannula. This resulted in the immediate formation of a dense intraluminal coagulum which extended from the aortic valve to beyond the aortic bifurcation and, as described previously,15 arrested aortic blood flow almost instantaneously. At the same time, the left carotid cannula was clamped and the animal was killed with an intravenous injection of concentrated KCl.

Following an extensive dorsal laminectomy, five segments of the spinal cord were procured at the following vertebral levels: C3-5, T3-5, T7-9, L1-2, and L-3 to the sacrum. The arterial blood and the cord samples were weighed (ranging from 30 to 90 mg), then they were solubilized for 48 to 72 hours and their radioactivity was determined by scintillation spectrophotometry. The regional SCBF's were then calculated using the equation:

\[ F_r = \frac{Q_a \cdot F_a}{Q_i \cdot M_i} \times 100, \]

where \( F_r \) is regional blood flow (ml · min⁻¹ · 100 gm⁻¹), \( F_a \) is the rate of external hemorrhage (ml · min⁻¹), \( Q_i \) is the indicator content in the tissue, \( Q_a \) is the indicator content in the shed arterial blood, and \( M_i \) is the sample weight (gm). The theoretical basis of this methodology and the derivation of the equation from the Fick principle are described in detail in previous publications.18

Experimental Groups

In all animal groups, MABP and arterial blood gases were measured just prior to the performance of flow measurements. Group A (normal control) consisted of seven rats. No technical interventions were made except those previously mentioned. Rectal temperature was 37.2° ± 0.3°C at the time of the flow measurements. Group B contained seven rats treated with corporal hypothermia. Following anesthesia and catheter placement, these rats were placed in an ambient temperature of 4°C until their body temperature was in the range of 25° to 30°C. Mean cold exposure time (± standard error of the mean) was 53 ± 6 minutes. Regional blood flow measurements were made immediately following withdrawal of these rats from the cold environment.

The seven rats in Group C received corporal hypothermia and hemorrhage. These rats were prepared and exposed to cold precisely as in Group B. However, arterial blood was withdrawn as necessary from the carotid cannula to maintain MABP at or near the control level of 126 mm Hg. Blood was withdrawn immediately prior to cold exposure, 15 minutes following cold exposure, and immediately prior to the performance of flow measurements. The mean volume of blood withdrawn was 6.8 ± 0.4 ml (21.0 ± 1.2 ml · kg⁻¹). The cold exposure time in this group was 54 ± 4 minutes.

Data Analysis

Data were analyzed using the Statistical Analysis System as implemented on the Washington University Mainframe IBM computer system. Results are reported as mean ± standard error of the mean. Means in the three groups were compared using the analysis of variance with the Bonferroni correction. A repeated-measures analysis of variance was used to compare the five levels of spinal cord measurements. The null hypothesis was rejected at \( p < 0.05 \).

Similar analyses were made of the tissue vascular resistances (R), which were calculated from the formula \( R = \frac{MABP}{F_r} \). The units are mm Hg · ml⁻¹ · min⁻¹ · 100 gm.

Results

In the Group A control animals, SCBF ranged from 68.5 ± 4.9 to 52.7 ± 5.4 ml · min⁻¹ · 100 gm⁻¹. There were differences among the flows at various cord levels, those in the two thoracic segments being the lowest (Table 1). These flow values are similar to those previously reported in pentobarbital-anesthetized rats,15 although in the present experiments, the highest flow was not at the "lumbar prominence" (L1-2), as was previously the case. The calculated vascular resistances were inversely related to the segmental blood flow, being greatest in the two thoracic segments in which regional blood flow was the least (Table 2).

In Group B animals, hypothermia induction was associated with a brisk rise in MABP to 165 ± 4 mm Hg. The SCBF was elevated by 52% to 69% in all cord segments. As in the control group, regional blood flows were lowest in the two thoracic cord segments. There were no changes in vascular resistance from control levels in any of the five segments, however, suggesting that an appreciable vasodilatory response had not occurred.

* Transducer, Model P23 ID, manufactured by Statham, Oxnard, California; pressure monitor, Model 414, manufactured by Textronic, Oregon.
† pH/Blood gas analyzer, Model 1301, manufactured by Instrumentation Laboratory, Lexington, Massachusetts.

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### TABLE 1

**Spinal cord blood flow (ml.min⁻¹.100 gm⁻¹) at five spinal cord levels in three rat groups***

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Spinal Cord Level of Sample</th>
<th>MABP (mm Hg)</th>
<th>Rectal Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1: Cervical</td>
<td>2: High Thoracic</td>
<td>3: Thoracic</td>
</tr>
<tr>
<td>A: control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: hypothermia</td>
<td>113.4 ± 10.6⁴</td>
<td>86.6 ± 7.7⁴</td>
<td>82.2 ± 7.9⁴</td>
</tr>
<tr>
<td>C: hypothermia &amp; hemorrhage</td>
<td>109.8 ± 11.8⁴</td>
<td>85.8 ± 9.4⁴</td>
<td>82.1 ± 7.9⁴</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for each group of seven rats. Significance of difference (within groups): a = p < 0.001 vs. 2, 3; b = p < 0.03 vs. 4; c = p < 0.001 vs. 2, 3, 4; d = p < 0.005 vs. 4. Significance of difference (between groups): e = p < 0.03 vs. A; f = p < 0.0001 vs. A, C; g = p < 0.0001 vs. A. MABP = mean arterial blood pressure.

The SCBF in the normotensive Group C rats was nearly identical to that in the hypertensive Group B rats in all five cord segments. As in Groups A and B, flows were least in the two thoracic segments. Vascular resistances were lower than control levels in all five cord segments. Rectal temperatures in Groups B and C did not differ significantly and both were lower than control levels. Arterial pCO₂ in Group C was less than in the control rats, but the remainder of the blood gas analyses were similar in all groups (Table 3). All groups were of similar body weight.

### Discussion

The regional blood flow to the brain in conscious or anesthetized rats remains relatively constant when MABP is raised or lowered through a wide range. This phenomenon, termed "hemodynamic autoregulation," occurs in several other tissues as well as in the brain. Although regional blood flow in the spinal cord has not been as fully studied as in the brain, there are several reports, including one from this laboratory, indicating that hemodynamic autoregulation through a similar range of arterial blood pressure also occurs in the spinal cord. ³, ⁵, ⁶, ⁷, ⁸, ¹⁵

The ¹⁴C-butanol indicator-fractionation method of Van Uitert and Levy ²² has been adapted, first for the measurement of peripheral nerve blood flow and subsequently for the measurement of SCBF. ¹⁵, ¹⁷, ¹⁹ This method is comparatively simple technically, is both sensitive and reproducible, and does not require invasion of the spinal cord. Spinal cord blood flow has also been shown to increase in response to arterial hypercarbia or hypoxemia and to decrease with hypocarbia, mirroring the hemodynamic response of the brain to these same conditions. The weight of available evidence, therefore, supports the view that both major components of the central nervous system share common blood flow regulatory mechanisms, at least under the conditions just enumerated.

Regional blood flow in the brain also decreases if the brain is cooled regionally or if systemic hypothermia is induced in anesthetized subjects; this presumably can be related to the decreased metabolic rate that results in tissues or organs when ambient temperature is beneath the physiological range (Q₁₀⁰ effect). ⁹, ¹⁴, ²⁶ There are numerous clinical reports of the use of corporal hypothermia in intracranial operative procedures such as aneurysmorrhaphy or the resection of tumors or vascular malformations. ²⁰, ²¹

Our previous investigations ¹⁹ have indicated that the response of regional blood flow in peripheral nerves to corporal hypothermia appears to differ from that in brain. Sciatic nerve blood flow was elevated 50% or more in anesthetized rats made hypothermic either by being placed in a cold environment or by surface cooling with ice-alcohol compresses. However, blood flow in peripheral nerves was unaffected by local nerve cooling in normothermic rats with rectal temperatures maintained by means of an external heat source.¹⁹ Those experiments were performed after the chance

### TABLE 2

**Spinal cord vascular resistance (mm Hg.ml⁻¹.min⁻¹.100 gm⁻¹) at five spinal levels in three rat groups***

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Spinal Cord Level of Sample</th>
<th>MABP (mm Hg)</th>
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<td></td>
<td>1: Cervical</td>
<td>2: High Thoracic</td>
<td>3: Thoracic</td>
</tr>
<tr>
<td>A: control</td>
<td>1.9 ± 0.2⁵</td>
<td>2.4 ± 0.2</td>
<td>2.5 ± 0.2⁶</td>
</tr>
<tr>
<td>B: hypothermia</td>
<td>1.5 ± 0.2⁴</td>
<td>2.0 ± 0.2</td>
<td>2.1 ± 0.2⁴</td>
</tr>
<tr>
<td>C: hypothermia &amp; hemorrhage</td>
<td>1.2 ± 0.3⁴</td>
<td>1.6 ± 0.4⁴</td>
<td>1.6 ± 0.4⁴</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means for each group of seven rats. Significance of difference (within groups): a = p < 0.01 vs. 2, 3; b = p < 0.03 vs. 4; c = p < 0.001 vs. 2, 3, 4. Significance of difference (between groups): d = p < 0.05 vs. A.

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observation that sciatic nerve blood flow was strikingly elevated in an anesthetized rat in which the body temperature had inadvertently been lowered to 25°C, and also prompted the present investigation, as SCBF has not previously been quantitated in hypothermic subjects.

In the present experiments, SCBF increased by an average of 59% when the body temperature was lowered. Hypothermia was associated with an increase in MABP to 165 ± 4 mm Hg from 126 ± 6 mm Hg in the control group. We and others have shown previously that SCBF increases in response to elevations of MABP beyond 160 mm Hg (that is, that hemodynamic autoregulation is not operative above this level of MABP). However, in the present experiments, when MABP was maintained at the control level by withdrawal of arterial blood in hypothermic rats, SCBF at the five levels at which it was measured was still nearly identical to that observed in the hypothermic, unbled hypertensive Group B rats. In the latter group, vascular resistance was not different from control findings at any level. In contrast, vascular resistance was less than control at all five cord levels in the Group C rats. These data suggest that hemodynamic autoregulation is impaired in the spinal cord in the presence of hypothermia, possibly because of a decrease in vascular tone.

Thus, although autoregulation is present through a similar range of MABP in both brain and spinal cord, our observations suggest that the response to the induction of corporal hypothermia may differ: blood flow increased in the spinal cord in our hypothermic rats. Brain blood flow was not measured in the present experiments, but the literature contains several reports that have demonstrated a decrease in blood flow in the brain in both man and other vertebrates after the induction of corporal hypothermia. Although peripheral nerves do not show evidence of hemodynamic autoregulation, their circulatory response to corporal hypothermia resembles what we now report in spinal cord, namely: regional blood flow is increased.

These observations indicate that impairment of autoregulation of blood flow occurs in the spinal cord following induction of moderate systemic hypothermia in rats anesthetized with pentobarbital. The present experiments provide no explanation for the mediation of the observed anomalous rise in regional SCBF. If this phenomenon also occurs in man, it might be advantageously employed to minimize the incidence of intraoperative ischemic injury to the spinal cord.

References


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