Loss of autoregulation and posttraumatic ischemia following experimental spinal cord trauma

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Blood flow in the dorsolateral funiculus of the cat thoracic spinal cord was studied after severe experimental cord injury, using a modification of the hydrogen clearance technique. Autoregulation was intact during the initial 60 to 90 minutes after cord injury, but was then lost coincident with the onset of ischemia. The data suggest that the ischemic response to spinal cord injury is mediated both by the loss of autoregulation and by relative vasoconstriction of the resistance vessels. Therapeutic intervention aimed at maintaining perfusion during the early posttraumatic period may prove of value in reversing or limiting some elements of dysfunction due to the secondary injury of ischemia.

KEY WORDS • spinal cord blood flow • spinal cord trauma • ischemia • autoregulation

THE factors responsible for the neural dysfunction following spinal cord trauma are not well delineated. Edema, metabolic changes, and alterations in spinal cord blood flow (SCBF) have all been suggested as on-going pathophysiological processes contributing to posttraumatic spinal cord dysfunction. 7,14,25 Several studies have investigated the changes in SCBF during the posttraumatic period and have concluded that, in certain models, ischemia 9,19,24,26 and not hyperemia 3,1,2 is the predominant vascular response of the white matter to severe cord injury. A recent study in this laboratory not only confirmed the presence of ischemia in the lateral white matter after severe thoracic cord trauma, but suggested that there was a consistent time delay between injury and demonstrable ischemia. 26 That study suggested that, although blood pressure fell within a few minutes after trauma, SCBF remained normal until 1 to 2 hours later. The present study investigates the hypothesis that ischemia of delayed onset is related to the loss of autoregulation.

Materials and Methods

Preparation of Animals

Measurement of blood flow by means of the hydrogen clearance technique is based on the detection of the current generated by the oxidation of hydrogen at the surface of a polarized platinum electrode implanted in the tissue. 1,21,25 In order to obtain reproducible data, we have refined the technique to include the following factors: 1) stabilization of the spinal column and dampening of negative intrathoracic pressure; 2) relatively atraumatic and stereotaxic placement of electrolytically etched platinum microelectrodes; 3) modifications in amplifier and recording circuitry; and 4) standardization of electrode resistance, impedance, and current from site to site and over time. These modifications are described in detail elsewhere. 25

Adult cats, weighing 3 to 5 kg were anesthetized with intraperitoneal pentobarbital (35 mg/kg), and artificially ventilated through a tracheostomy on a Harvard respirator* with 50% O2 and 50% nitrous oxide gas. A femoral vein was cannulated for administration of Flaxedil (3 mg/kg/hr). A femoral artery was cannulated for monitoring of blood pressure and arterial blood gases. Respiratory end-tidal CO2 and core temperature were continuously monitored and maintained in physiological ranges. All experiments were performed under control conditions of pO2 > 90 mm Hg, pCO2 32 to 38 mm Hg, and temperature of 38° ± 1.5° C.

A dorsal laminectomy was performed from T4-7 leaving the dura intact, and the cat was placed in a Kopf spinal stereotaxic holder.† A chest tube was

* Harvard respirator manufactured by Harvard Apparatus, 150 Dover Road, Millis, Massachusetts.
† Kopf stereotaxic holder manufactured by David Kopf Instruments, 7324 Elmo Street, Tujunga, California.
Autoregulation and ischemia in cord trauma placed to dampen negative intrathoracic pressure and further diminish cord motion. Platinum recording electrodes (200 μ in diameter) were placed stereotaxically in the dorsolateral funiculus of the exposed spinal cord. The laminectomy site was filled with mineral oil and a micro-thermistor placed in the epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against the platinum recording electrode with 650 mV against epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against epidural space to record temperature. After polarizing the platinum recording electrode with 650 mV against the platinum recording electrode with 650 mV against

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Experimental Groups

The cats were divided into four groups as follows:

- **Group A** = control non-trauma (five cats)
- **Group B** = control trauma (10 cats)
- **Group C** = control autoregulation (five cats)
- **Group D** = trauma autoregulation (five cats).

The non-traumatized control series (Group A) consisted of five cats; SCBF measurements were obtained at 45-minute intervals for 6 hours from two sites 1 cm apart. The trauma series (Group B) consisted of 10 cats prepared as above. Three to five control SCBF measurements were obtained in each cat 1 cm above the proposed site of trauma (T-6). Both electrodes were removed and a 500 gm-cm lesion was inflicted by a 20-gm weight dropped from a 25-cm height. Electrodes were reimplemented at the level of trauma and 1 cm below trauma. For the next 6 to 7 hours, SCBF measurements were obtained at 45- to 60-minute intervals.

The control autoregulation series (Group C) consisted of five cats; multiple blood-flow measurements were obtained at different levels of systemic arterial pressure (mSAP). After three to five flows had been measured at normal blood pressure, mSAP was elevated by Harvard pump infusion of Aramine (metaraminol bitartrate), or lowered by infusion of nitroprusside.

The trauma-autoregulation series (Group D) consisted of five animals prepared as in Group B. After the 500 gm-cm injury was inflicted at T-6, the blood pressure was allowed to stabilize at its new lower level for 10 minutes, then was elevated back to its pretrauma blood pressure by Aramine infusion. Thereafter, SCBF determinations were obtained for 3½ hours. At this time blood pressure was lowered with nitroprusside to 50 mm Hg, SCBF was measured, then mSAP re-elevated with Aramine. Blood-flow measurements were then obtained for another hour.

In all series, the cats were sacrificed by perfusion with formalin, and the cords removed for histological examination of the electrode sites and the cord-trauma sites.

**Results**

**Control and Trauma Series**

The results of the control (Group A) and 500 gm-cm trauma (Group B) series have been presented in detail previously, and will only be summarized here. Based on 51 sequential determinations in five cats, the SCBF in the dorsolateral funiculus of thoracic cord was $10.99 \pm 0.89$ ml/100 gm/min, with no significant variation over a 7-hour period. This correlates well with the average of 38 pretrauma control flows of $11.13 \pm 1.12$ ml/100 gm/min, from the traumatized series (Group B). The 500 gm-cm injury at T-6 consistently produced an initial hypertensive response lasting 3 to 5 minutes, followed by a gradual fall in blood pressure to 30 to 40 mm Hg lower than the pretrauma blood pressure. The mSAP therefrom remained approximately at this level for the duration of the experiment (see lower graphs in Fig. 2).

A typical monoexponential clearance curve and semilog transposition from a pretrauma control flow is seen in Fig. 1 A; Fig. 1 B shows the clearance curve and transposition obtained from the same animal 4 hours after 500 gm-cm trauma, recorded at the level of trauma. Figure 1 C is the histological demonstration of the recording site at the level of injury.

The average SCBF measurements obtained in 10 cats, recorded at the level of trauma, is presented in Fig. 2 left. The SCBF did not differ significantly from controls for the first hour after trauma but was significantly reduced at subsequent time periods ($p < 0.005$). The average mSAP before trauma was 120 mm Hg. After a short hypertensive response to trauma, mSAP fell an average of 30 to 40 mm Hg to 80 mm Hg, and remained low for the duration of the experiment. Although mSAP fell within 10 minutes of trauma, SCBF did not fall until 1 to 2 hours later. At a site 1 cm below the site of trauma (Fig. 2 right), SCBF did not fall to statistically significant ischemic levels until nearly 2 hours after trauma, although again mSAP fell within 10 minutes to between 30 and 40 mm Hg below the pretrauma blood pressure.

**Control-Autoregulation Series**

The blood-flow measurements (and their monoexponential semilog transpositions) made at blood pressures of 50, 100, 150, and 200 mm Hg in a non-traumatized cat (Group C) are shown in Fig. 3.
FIG. 1. A: Monoexponential washout curve of a typical pretrauma control flow and its semilog transposition. Spinal cord blood flow (SCBF) was 9.77 ml/100 gm/min. B: Clearance curve at 4 hours after 500 gm-cm trauma, recorded at the level of trauma (T-6), and its semilog transposition showing a monoexponential decay. The SCBF was 6.90 ml/100 gm/min. C: Histological section from the recording site from which B was obtained, showing central hemorrhagic necrosis. The arrow indicates the electrode tract.

Flow values were 8.72, 11.40, 13.27, and 17.85 ml/100 gm/min, respectively. The data obtained in these five cats, which had blood pressures manipulated as described in Methods section, are summarized in Fig. 4. In two of the cats, only a single electrode was functioning. It is evident that all cats regulated blood flow fairly well below 90 mm Hg, but most animals had virtually no autoregulation above this blood pressure. Below 40 mm Hg, SCBF fell so precipitously that no accurate washout curve could be obtained in any animal. Blood flow was plotted against blood pressure for intervals of 10 to 15 mm Hg, and a best fit calculated by computer. Autoregulation was intact only when blood pressure was between 40 and 90 mm Hg (Fig. 4).

Trauma-Autoregulation Series

Clearance curves with their semilog transpositions are shown for Group D cats before trauma, and at 1 and 3½ hours after trauma when blood pressure has been elevated to pretrauma levels by infusion of Aramine (Fig. 5). The histology of the recording site for this experiment is demonstrated in Fig. 5 D.

Figure 6 shows the average SCBF measurements recorded at trauma in the five cats in Group D, and the average blood pressure (mSAP) at each time point, with both the posttraumatic hypotension and the episode of nitroprusside-induced hypotension indicated. It is evident from the graphs and the Student's t-test values that blood flow did not become significantly different from that of the control-trauma series (Group B) for over 1 hour. Thereafter, SCBF in the normotensive series was significantly higher than in Group B (p < 0.001). When the blood pressure was lowered to 50 mm Hg by nitroprusside infusion, ischemia was reproduced but the SCBF was so slow (less than 5 ml/100 gm/min) that no exact value could be ascribed to this point. When blood pressure was again elevated, a return to the increased level of SCBF was seen (p < 0.001). After this episode of hypotension, there was no significant decrease in SCBF. Therefore, a postischemic "no-reflow" phenomenon was not seen in this model at the level of the most severe injury with this period and degree of hypotension.

At 1 cm below the trauma site (Fig. 6 right), SCBF was not different from the control-trauma series (Group B) until nearly 2 hours after trauma; then it was statistically higher (p < 0.001). After the episode of nitroprusside-induced hypotension, SCBF was transiently increased, but this was not statistically significant (p > 0.1). In this model, therefore, postischemic hyperemia did not occur at a site 1 cm below the point of maximum injury in the lateral column.

We were aware of the possible association between increased blood flow and increased hemorrhages in the gray and white matter, but were not able to make a definite histological association between these two parameters when comparing the trauma-hypotensive to the trauma-normotensive series.

Discussion

In the previous series of experiments, our modification of the hydrogen clearance technique was
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Fig. 2. Upper Graphs: Percentage changes of spinal cord blood flow (SCBF) against time, recorded at the level of trauma (left), and simultaneously 1 cm below trauma (right). A 500 gm-cm trauma was inflicted at time 0. Each animal is compared to its own pretrauma control flows. The vertical lines indicate the standard deviation, and the two-tailed Student's t-test for each point (p value) is compared to control flows over a similar time period from the control series (Group A). Lower Graphs: Simultaneous blood-pressure (mSAP) changes after trauma at 15-minute intervals.

Demonstrated to be reliable, reproducible, and able to measure blood flow from small regions of homogeneous tissue in the spinal cord. Initial studies using that technique showed that in response to 500 gm-cm trauma, ischemia occurred both at the level of trauma and 1 cm caudal in the dorsolateral funiculus of the thoracic spinal cord. However, it was noted that while mSAP fell an average of 30 to 40 mm Hg within 10 minutes after trauma, SCBF was maintained until 1 to 2 hours later. This series of experiments was designed to investigate some aspects of autoregulation both in the maintenance of SCBF during the early posttraumatic period and in the delayed onset of ischemia.

In the cerebral vasculature, the ability to maintain blood flow despite changes in both intracranial pressure and blood pressure (autoregulation) is well known, although the mechanisms that mediate the compensatory changes in the vascular resistance in response to changes in blood pressure are not well understood. In the intact spinal cord, autoregulation has been documented by two investigators. Kobrine, et al., found a range of intact autoregulation when mSAP was between 50 and 135 mm Hg. Griffiths recorded a range of intact autoregulation from 60 to 150 mm Hg. Both studies, however, induced hypotension by phlebotomy, which changes blood viscosity, hematocrit, and circulating blood volume, all of which may influence vascular resistance and blood flow. Hypertension was induced either by norepinephrine, which is known to decrease cerebral blood flow, or angiotension, which also has a direct sympathomimetic effect on the central nervous system (CNS). Aramine was used in our study because it is thought to act as a peripheral vasoconstrictor without CNS effects. Nitroprusside is believed to be purely a peripheral vasodilator with no known effect on blood viscosity.

Our data are not in agreement with either previous study. Autoregulation in the dorsolateral funiculus of the thoracic cord was present in most animals only when blood pressures were within the narrow range of 40 to 90 mm Hg (Fig. 4 right). Even within this range there was a tendency for blood flow to vary passively with blood pressure, but this was not as marked as at pressures greater than 90 mm Hg (Fig. 4). In addition,
Fig. 3. Clearance curves and semilog transpositions in a cat representative of Group C. A: At systemic arterial pressure (mSAP) of 50 mm Hg, the spinal cord blood flow (SCBF) was 8.72 ml/100 gm/min. B: At mSAP of 100 mm Hg, the SCBF was 11.40 ml/100 gm/min. C: At mSAP of 150 mm Hg, the SCBF was 13.27 ml/100 gm/min. D: At mSAP of 200 mm Hg, the SCBF was 17.35 ml/100 gm/min.

Fig. 4. Spinal cord blood flow (SCBF) measured against systemic arterial pressure (mSAP) for the individual cats in the control-autoregulation series. Left: Actual values; similar symbols represent different electrode sites in the same animal. Two animals had only one electrode recording blood flow. Right: Summary of data shown left.
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Fig. 5. A-C. Clearance curves and semilog transpositions in a cat representative of Group D. A: Recording before 500 gm-cm injury, the spinal cord blood flow (SCBF) was 16.54 ml/100 gm/min. B: One hour after trauma, when systemic arterial pressure (mSAP) had been maintained at pretrauma levels by Aramine infusion, the SCBF was 16.06 ml/100 gm/min. C: Four hours after trauma, with blood pressure elevated, the SCBF was 19.82 ml/100 gm/min. D: Histological section from the recording site showing central hemorrhagic necrosis. The arrow indicates the electrode tract.

The response to blood pressure greater than 90 mm Hg was highly variable (Fig. 4 left). Whether this represents different populations in our experimental groups or the influence of other factors during the experiment is not known. One possible source of error is the drug administration itself. Aramine was used in this study because it is thought to act as a peripheral vasoconstrictor with no effect on CNS vasculature, but the lack of autoregulation to hypertension may be due to a direct effect on the spinal cord vessels. Similarly, nitroprusside, acting as a peripheral vasodilator, may itself lower SCBF, and thereby alter autoregulation to low blood pressure. Unlike the cerebral vasculature with its blood supply from high-volume, high-pressure vessels (that is, carotid and vertebral vasculature), autoregulation in the spinal cord may not regulate blood flow to any but frankly hypotensive blood pressures.

The trauma-autoregulation series of experiments (Group D) demonstrated that autoregulation, in the range that we measured it, was intact during the initial posttraumatic period (Fig. 7). Although mSAP fell 30 to 40 mm Hg within 10 minutes after trauma, SCBF was maintained for over 1 hour. If mSAP was elevated back to normal during this time, SCBF did not increase further. This implies that in the trauma-hypotensive and trauma-normotensive series, autoregulation was intact during the first hour at the level of trauma and for nearly 2 hours 1 cm below trauma. After this point, however, if the blood pressure was returned to its low level, ischemia occurred in all cats. If the blood pressure was elevated with Aramine, SCBF increased dramatically (p < 0.001) at both electrode sites, indicating loss of autoregulation. Four hours later, nitroprusside-induced hypotension reproduced severe ischemia. Return of mSAP to normal did not induce either thrombosis (the "no-reflow" phenomenon) at the level of trauma, nor reactive hyperemia 1 cm below. The data therefore suggest that, in our model, autoregulation is lost on a delayed
basis after experimental cord trauma and that it may be a factor responsible for posttraumatic ischemia in the white matter.

What happens in vivo to the resistance vessel when autoregulation is lost is not known. The vessel may be fixed in a mid-position or dilated state or may in fact be responding passively to changes in transmural pressure. Figure 7 suggests one possible mechanism. In the spinal cord, where negligible venous pressure is assumed, the relationship between flow, pressure, and resistance is described by: Flow = Pressure/Resistance, or SCBF = mSAP/R.

During the first 60 to 90 minutes after trauma (Phase 1), autoregulation is intact. Flow is constant, but blood pressure has fallen, so resistance must be decreased (that is, vasodilation of the resistance vessel has occurred). After this initial period, autoregulation is lost (Phase 2). Flow is decreased, blood pressure remains low, so vascular resistance must be greater than during Phase 1 (mid-position or vasoconstriction of resistance vessel). This explanation supports the ischemic concept of posttraumatic SCBF. How these vascular changes are mediated is unknown. Reivich, et al., 23 and Bruce, et al., 5 have shown that after cerebral trauma, autoregulation is lost in a highly focal pattern, implying local control of autoregulation. Kobrine, et al., 15 have demonstrated no significant loss of autoregulation after section of the cervical cord, implying local control of autoregulation (that is, metabolic or myogenic) in the spinal cord. Further studies suggested alpha and beta adrenergic innervation of spinal cord resistance vessels. 17, 18 In the present study, the loss of autoregulation at different intervals after cord trauma at the two electrode sites also suggests local control of autoregulation. The delay in onset of ischemia coincident with the loss of

Fig. 6. Percentage change against time in spinal cord blood flow (SCBF) at the level of trauma (left), and simultaneously at 1 cm below trauma site (right), when the posttraumatic blood pressure had been returned to normal by Aramine. Each animal is compared with its pretrauma levels. Trauma was inflicted at time 0. The vertical lines represent standard deviation, and the two-tailed Student's t-test for each point (p values) compare SCBF against data from the control-trauma series (Group B) (see Fig. 2). The average values for systemic arterial pressure (mSAP) at 15-minute intervals are presented below.
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Autoregulation might be explained on the basis of release of certain vasoactive substances. Norepinephrine,6,7,20 serotonin,4 and dopamine20 have been suggested as mediators of posttraumatic ischemia. These same substances might be involved in the loss of autoregulation. It is also possible that the delayed loss of autoregulation is secondary to decreased metabolic and energy-producing activity of the injured cord.22 Whether in the non-traumatized cord or during the first 60 to 90 minutes after cord trauma, intact autoregulation to low blood pressure may involve an active, energy-dependent, vasodilation while the loss of autoregulation after trauma may involve a passive, energy-independent, response to transmural pressure. Therefore, at normotensive blood pressures, the resistance vessel may be in mid-position, similar to what has been proposed for the cerebral vasculature.

The same dependency of blood flow on systemic arterial pressure has been demonstrated in cerebral ischemia3,28,20 and vasospasm studies.19 In areas of cerebral ischemia with impaired autoregulation, induced hypertension has restored cortical electrical activity, cell-membrane function, ionic K-Na adenosine triphosphate (ATP)-dependent pumping mechanism, and neurological function.12 A similar situation may be present in the ischemic traumatized spinal cord.

The role of blood pressure in posttraumatic patterns of SCBF has not been investigated or emphasized previously in the literature. Possibly differences in mSAP in different animal models may account for some of the conflicting literature on posttraumatic alterations in SCBF. It is clear that studies that do not specify blood-pressure alterations and manipulations are subject to misinterpretation and confusion. Clinically, if alterations in posttraumatic SCBF do constitute a cause of secondary injury, then the maintenance of normal blood pressure during the posttraumatic period of "spinal sympathetic shock" might be indicated in selective cases. Extensive testing of this hypothesis in the laboratory would of course be necessary before any clinical application could be suggested.

**Conclusions**

1. Ischemia is the predominant lateral white-matter vascular response to severe experimental spinal cord injury when blood pressure is not manipulated.
2. The ischemia is delayed in onset for 1 to 2 hours after trauma.
3. Autoregulation is intact during the initial posttraumatic period, and is then lost coincident with the onset of ischemia.
4. The ischemic response may be mediated both by lost autoregulation and by relative vasoconstriction of the resistance vessels.

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**References**


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