The histopathology of experimental spinal cord trauma

The effect of systemic blood pressure

Stephen E. Rawe, M.D., William A. Lee, B.S., and Phanor L. Perot, Jr., M.D., Ph.D.

Department of Neurosurgery, Medical University of South Carolina, Charleston, South Carolina

The early sequential histopathological alterations following a concussive paraplegic injury to the posterior thoracic spinal cord in cats were studied. The lack of significant progression of hemorrhages over a 4-hour period after injury indicates that most hemorrhages probably occur within the first hour. The marked enhancement or retardation of hemorrhages in the post-injury period, when the blood pressure was increased or decreased, respectively, demonstrates the loss of autoregulation of spinal cord vasculature at the trauma site after a concussive paraplegic injury. Progressive edema formation was evident over a 4-hour period following injury, and it could be enhanced or retarded by elevation or reduction of the systemic blood pressure.

Key Words □ experimental spinal cord injury □ blood pressure □ hemorrhage □ autoregulation □ neuronal and axonal changes □ edema

A recent study reports that the degree of hemorrhagic involvement in both gray and white matter following an experimental, paraplegic concussive injury to the posterior spinal cord in cats could be correlated with the systemic blood pressure at 1 hour post-injury. A study was designed to investigate the histopathological changes that occurred from 1 to 4 hours when the systemic blood pressure was altered after injury.

Materials and Methods

Adult cats weighing between 2.5 and 3.5 kg were used in this study. All animals were anesthetized with pentobarbital (35 mg/kg) intraperitoneally. A tracheostomy was performed, and respirations were controlled by a small animal ventilator. A femoral artery and vein were cannulated for monitoring of systemic blood pressure and for the administration of intravenous fluids. The endtidal tracheal pCO₂ was monitored and controlled between 2% and 4%. Body temperature was maintained at 36° to 38° C. The somatosensory cortical evoked potential (SEP) was recorded by stimulation of the lower extremities as described by D’Angelo, et al.

Histopathological changes in 34 cats were studied over a 1- to 4-hour period. A laminectomy was performed from T2-6, and trauma was administered at the T-5 segmental level by dropping a 25-gm weight 20 cm onto a contoured impounder resting on the exposed posterior dura. This injury force has con-
The histopathology of experimental spinal cord trauma

Consistently produced permanent paraplegia in our experimental animals. The animals were divided into three groups according to their post-traumatic blood pressure. Fourteen animals remained normotensive (80 to 120 mm Hg) following injury. In the hypotensive group of animals, 14 cats had their blood pressure temporarily lowered to between 40 and 50 mm Hg by the administration of 2% to 4% halothane before trauma in order to evaluate the presence of the SEP. The blood pressure was then allowed to return to normal levels until 15 minutes after injury. At this time, systolic blood pressure was once again lowered to between 40 and 50 mm Hg, and allowed to remain at this level for the duration of the experiment. In the hypertensive group of animals, six cats had their systolic blood pressure increased to greater than 150 mm Hg by intravenous Aramine (metaraminol bitartrate) before injury in order to evaluate the presence of the SEP. The blood pressure was then allowed to return to normal levels until 15 minutes after injury, when it was again elevated to hypertensive levels. The animals were sacrificed at 1 hour, 2 hours, or 4 hours after injury.

At the termination of the experiment, the animals were sacrificed by transection of the great thoracic vessels. The traumatized section was removed, placed in 10% formalin, and subsequently sectioned in 30-μ segments, and stained with hematoxylin and eosin (H & E). Histological sections of the traumatized cord segment and nontraumatized segments above and below the areas of trauma were observed without prior knowledge of the post-traumatic blood pressure. The quantitation of hemorrhages was performed by a Lovins field finder* under medium power (× 40).

**Results**

An SEP from stimulation of the posterior tibial nerve was recorded in all animals before trauma and was present at hypotensive and hypertensive ranges during the test responses to halothane and Aramine, respectively. After trauma, the SEP was absent in all animals and had not returned by the time of sacrifice. A pressor response to spinal cord trauma was observed in all animals.

The injury force in this experimental design invariably produced subarachnoid hemorrhage and contusion of the posterior surface of the cord. At 1 hour, hemorrhages were visualized in the gray and white matter. Hemorrhages in the latter area were predominantly localized in the perigray area, but were also randomly scattered throughout the peripheral white matter. Lateralization of hemorrhages in the gray and white matter was observed on the side of the cord when the impact was not imparted to the center of the posterior surface.

Quantitatively, hemorrhagic involvement of the gray matter was 50%, and white matter was 6% for normotensive animals (Table 1). By 4 hours, hemorrhages had increased, but not significantly from 1 hour, to 61% for gray and 10% for white matter, and there appeared to be greater coalescence of hemorrhages. In the hypotensive group of animals, there was a marked reduction of hemorrhages which did not increase significantly by 4 hours (Fig. 1, Table 1). Coalescence of hemorrhages was less in the 4-hour hypotensive animals than 4-hour normotensive ones. Hypertensive animals demonstrated a marked increase in hemorrhages at 1 hour, and extensive hemorrhagic involvement was noted throughout the white matter including the peripheral areas (Fig. 1, Table 1). No significant increase of hemorrhages was observed at 2 hours. Four-hour hypertensive animals were not considered valid because of the inability to maintain an elevated systemic blood pressure for that period of time.

High-power observation of sections from normotensive animals revealed that many neurons were obscured and encrusted by red blood cells. Those neuronal cell bodies which were visualized were either angulated and shrunken or swollen. Except for somewhat greater coalescence of hemorrhages in the central gray matter, similar changes were observed at 4 hours in the normotensive animals. Severe neuronal changes were also evident in the hypotensive group of animals at all time periods. However, these changes appeared to be less marked than those of normotensive animals and more neurons were visualized. In the hypertensive group of animals, neuronal changes were severe, and the majority of neuronal cell bodies were obliterated by hemorrhages.

Axonal swelling was evident throughout

---

S. E. Rawe, W. A. Lee and P. L. Perot, Jr.

### TABLE 1

<table>
<thead>
<tr>
<th>Blood Pressure Group</th>
<th>Post-Injury</th>
<th>1 hr</th>
<th>2 hrs</th>
<th>4 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive cats</td>
<td></td>
<td>66*</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>mean hemorrhages (%)</td>
<td></td>
<td>11</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No. cats</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Normotensive cats</td>
<td></td>
<td>50*</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>mean hemorrhages (%)</td>
<td></td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>No. cats</td>
<td></td>
<td>4</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hypotensive cats</td>
<td></td>
<td>12*</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>mean hemorrhages (%)</td>
<td></td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>SEM</td>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>No. cats</td>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*There was a significant difference between the hypertensive and hypotensive cats, and between the normotensive and hypotensive cats; p < 0.001.

---

**Fig. 1.** Sequential pathological cord sections after injury. *Left:* One hour. *Center:* Two hours. *Right:* Four hours. *Top Row:* Hypertensive. *Middle Row:* Normotensive. *Bottom Row:* Hypotensive. H & E, × 7.
The histopathology of experimental spinal cord trauma

the white matter at 1 hour in normotensive animals. An increase in periaxonal spaces was also present and appeared most marked in the anterior funiculi near the anterior median fissure, posterior perigray, and in the medial three-fourths of the lateral funiculi. An increase in extracellular space was evident in the central gray, anterior and posterior perigray, and in the posterior columns. Although periaxonal space enlargement was not as marked in the posterior columns, swelling and disruption of normal axonal organization underlying the areas where the main force had been imparted was apparent. Posteriorly, the pia-arachnoid was disrupted, and occasional polymorphonuclear cells and red blood cells were observed in the periphery of the white matter. Normal axonal structures were best observed in the peripheral white of the anterior and lateral funiculi. By 4 hours, axonal swelling and periaxonal spaces had increased and were now more apparent in the periphery of the anterior and lateral funiculi. In hypotensive animals, these changes were not as prominent as the normotensive animals. The changes in the 4-hour hypotensive animals were less than the alterations observed in the normotensive animals at 1 hour after injury. In contrast, hypertensive animals demonstrated a greater increase in periaxonal clear spaces, axonal swelling, and extracellular space than was observed in the normotensive animals at similar time periods.

Discussion

The finding of only a slight increase in gray and white matter hemorrhages following a concussive paraplegic injury to the spinal cord indicates that the majority of hemorrhages occurred during the first hour following trauma. Although coalescence of hemorrhagic sites was apparent at later time periods, there did not appear to be a significant progression of the hemorrhagic involvement from central gray to the peripheral white matter. Ultrastructural studies and microangiographic studies suggest that the hemorrhages are the result of shearing forces exerted on microvasculature by mechanical trauma.1,4

This study confirmed earlier observations that the severity of hemorrhagic involvement, particularly in the central gray at 1 hour after injury, could be correlated with the post-traumatic systemic blood pressure.20 The ability to markedly retard or enhance hemorrhagic involvement by lowering or raising systemic blood pressure when the force of injury is kept constant is related to vascular damage in gray and white matter, and to the absence of autoregulation of spinal cord blood flow. This study histopathologically demonstrated the loss of autoregulation in the area of trauma over a 4-hour period following a concussive paraplegic injury. A relative lack of hemorrhages in the peripheral white matter of normo- and hypotensive animals does not exclude vascular damage to this area. This is demonstrated by a marked increase in hemorrhages in the peripheral white matter in hypertensive animals. Griffiths and Miller8 have demonstrated altered vascular permeability in the spinal cord at the site of injury with the use of Evans blue albumin (EBA). Although extravasation of this fluorochrome dye was not apparent in the peripheral white matter, staining of the vascular wall was. Localization of this dye is probably in the endothelial basement membrane,19 and its presence is the first indication of vascular abnormality.21 Despite this vascular abnormality, significant perfusion of injured vasculature was present in the outer two-thirds of the peripheral white matter as visualized by thioflavine S, a dye that stains the endothelium of blood vessels through which it perfuses.8 The degree of trauma used in this experimental design most likely produces a significant vascular injury throughout the white matter; however, because of its location and orientation, white matter vascularity, particularly in the peripheral areas, may be more resistant to traumatic injury than gray matter vascularity.

Autoregulation of spinal cord blood flow (SCBF) has been documented by several investigators in uninjured dogs and monkeys.7,13,15 Although studies of autoregulation by means of quantitative SCBF determinations have not been measured in the post-injury cord, trauma might be expected to result in its impairment or absence. Impaired or abolished autoregulation from trauma may result in increased susceptibility of vasculature to mechanical disruption by sudden increases of perfusion pressure when Aramine is administered. Markedly increased hemorrhagic involvement throughout the gray and
white matter, even in peripheral white matter areas, occurred in this study when the animals were hypertensive after injury. This is probably secondary to rupture of already damaged endothelial tight junctions. However, the lack of hemorrhagic involvement in nontraumatized cord segment indicates that hemorrhages are not solely related to systemic blood pressure elevation by Aramine.

Halothane, a known cerebral vasodilator, and results in a decrease in cerebral oxygen demand. Although the vasodilatory effect of halothane might be expected to be beneficial to cord perfusion, the use of 2% to 4% concentrations in this study results in such significant hypotension that blood flow is probably not increased, and vessels are usually maximally dilated by the hypotension alone. The absence of autoregulation and the existence of a hypotensive blood pressure following injury most likely result in a decrease of perfusion and account for the diminution of hemorrhages from injured vasculature. Impairment of autoregulation by this agent could be further detrimental if blood pressure is raised too rapidly.

Neuronal changes were severe at all time periods following injury regardless of blood pressure. The neuronal cell population observed in the hyper- and hypotensive animals appeared to be partly related to the amount of central hemorrhages that were present. Greater hemorrhages in the hypertensive animals increased the severity of neuronal changes while less severe changes were observed in the hypotensive animals with less hemorrhages.

The progressive increase in periaxonal clear spaces, axonal swelling, and extracellular space over a 4-hour period is probably secondary to progressive edema formation. Edema formation could be retarded or enhanced by alterations of systemic blood pressure following traumatic injury. Hypotensive preparations displayed less increase in periaxonal spaces and axonal swelling for corresponding time intervals than did normotensive ones. Hypertensive preparations conversely demonstrated earlier increases in periaxonal spaces and axonal swelling. Klatzo, et al. have demonstrated in a study of cold-injury edema that systolic blood pressure plays a significant role in the enhancement or retardation of edema formation. An outpouring of serum and red blood cells from disruption of microvasculature as a result of direct mechanical injury may significantly contribute to the increase in extracellular space. It appears that two mechanisms are responsible for the accentuation of edema formation as early as 1 hour following injury in the peripheral white matter of hypertensive animals. Edema formation centrally may be enhanced by the elevation of systemic blood pressure with a more rapid progression to the peripheral white matter. Also, altered vascular permeability and/or disruption of peripheral vasculature as evidenced by the presence of hemorrhages most likely lead to early edema formation in these peripheral areas. The less pronounced histopathological changes in periaxonal clear spaces and axonal swelling in the hypotensive preparations may be the result of retardation of edema formation from a low systolic blood pressure and less disruption of peripheral vasculature as evidenced by the lack of hemorrhages in the white matter.

The results of this study suggest that elevation of the systemic blood pressure in the post-injury period after a concussive-type spinal cord injury may be harmful. Disruption of already damaged vasculature with increased hemorrhages and enhancement of edema formation may result. However, lowering the blood pressure in order to retard hemorrhages and edema formation might prove deleterious in that ischemic changes in the white matter vasculature may occur in the presence of an impaired autoregulation of spinal cord white matter vasculature. The maintenance of a normotensive range of blood pressure is probably optimal in the treatment of acute spinal cord injury.

References
The histopathology of experimental spinal cord trauma


This work was supported by NINCDS Spinal Cord Injury Grants NS 10174-02 and 10174-03.

Address reprint requests to: Stephen E. Rawe, M.D., Medical University Hospital, Department of Neurosurgery, 171 Ashley Avenue, Charleston, South Carolina 29403.