Cerebrospinal fluid lactate and electrolyte levels following experimental spinal cord injury

DOUGLAS K. ANDERSON, PH.D., LEON D. PROCKOP, M.D., EUGENE D. MEANS, M.D., AND LAWRENCE E. HARTLEY, B.S.

Research Service, Veterans Administration Hospital, and Department of Physiology and Neurology Section, Department of Medicine, University of South Florida College of Medicine, Tampa, Florida

Cerebrospinal fluid (CSF) lactate, sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺), magnesium (Mg²⁺), and chloride (Cl⁻) levels were determined for 17 to 21 days following experimental spinal cord compression in cats. Laminectomies were performed at L-2 under general anesthesia with aseptic techniques. Paraplegia was produced by applying a 170-gm weight transdurally for 5 minutes. Significant increases in CSF lactate levels were observed on the first through ninth days post injury with peak levels (50% above normal) occurring at Day 5. The only significant postinjury CSF electrolyte changes were elevation in Ca²⁺ concentration on Days 3, 9, 11, 13, and 15, elevation in K⁺ concentration on Days 9 and 11 and decline in Cl⁻ levels on the first day. The CSF K⁺ increase probably reflected cellular loss of K⁺ from damaged tissue whereas the Ca²⁺ rise may have resulted from increased CSF protein levels. The prolonged elevation of CSF lactate indicates that tissue hypoxia plays a role in spinal cord compression paralysis, and that there is a continuing hypoxia of metabolically active spinal cord tissue for several days post injury.

KEY WORDS spinal cord injury cerebrospinal fluid lactate electrolytes

It is now generally agreed that cerebrospinal fluid (CSF) is in direct equilibrium with and reflects the composition of the central nervous system (CNS) extracellular fluid (ECF). Thus, analysis of CSF can provide an index of CNS metabolism in normal and diseased states. Examination of various CSF components has been used to provide direct diagnosis of a number of clinical conditions and to determine prognosis of and to guide therapy in cerebral disease or injury. For example, CSF lactate levels are elevated after head injury and may reflect the degree of cerebral damage. With the exception of a study by Bulat, et al., describing a decline in lumbar CSF concentrations of 5-hydroxyindolacetic acid 19 days after spinal cord trauma in cats, no investigative work in this area concerning spinal cord disease or injury has previously been performed. Recent reports of lactate and electrolyte alterations in injured spinal cord tissue suggest that CSF analysis following spinal cord...
trauma might be useful in the further study of spinal cord metabolic and/or biochemical changes attending spinal cord injury. The present studies were performed to determine whether experimental spinal cord compression caused significant changes in CSF lactate and electrolyte levels.

Methods and Materials

For this study we used immunized and conditioned female mongrel cats ranging in weight from 2.3 to 4.6 kg. They were divided into two groups: one group underwent experimental injury and the other comprised operative controls.

Experimental Injury Animals

All animals were anesthetized with intraperitoneal (IP) pentobarbital sodium (40 mg/kg) and intubated to maintain a patent airway. A polyethylene cannula was placed in the abdominal aorta by way of a femoral arteriotomy in order to monitor blood pressure and to obtain samples for blood gas and pH analysis. Ventilation was not assisted unless abnormal blood gas and pH values were obtained. A femoral vein was cannulated for administration of supplemental doses of anesthesia and other drugs as necessary. Rectal temperature was measured, and body temperature maintained between 36° and 38° C with a heating pad. The cats were immobilized in a stereotaxic frame, a one-segment laminectomy was performed at L-2, and the epidural fat was removed to expose the dura mater. Spinal cord trauma was induced using a modification of the compression model described by Waggener and Richardson and Nakamura. This method involved placing a known weight, extradurally, on the spinal cord for a prescribed length of time. The injury apparatus was a stainless steel rod (tip, 6 mm in diameter) that could be weighed as desired. The rod passed through a guide tube which was carefully positioned directly over and perpendicular to the center of the spinal cord thereby producing compression. Succinycholine chloride (1 mg/kg) was administered intravenously just prior to compression to prevent movement once compression was initiated. All animals were mechanically ventilated during this period of muscle paralysis. The wound was closed in layers and the animals were given intramuscular procaine penicillin (22,000 units/kg) on the day of surgery, and then every other day for 1 week postoperatively. In addition, the animals were given subcutaneous 5% dextrose in Ringer's solution (10 cc/kg) daily postoperatively until they were alert and feeding.

With this model, either reversible or irreversible paraplegia can be produced depending upon the magnitude of the weight and the duration of compression. For this study reversible paraplegia was produced by a 5-minute compression with 170-gm weight. The injury was characterized by varied return of weight-bearing and walking 2 to 4 weeks post injury. This magnitude of weight and duration of compression was chosen because it allowed repeated withdrawals of CSF from the lumbar subarachnoid space and eliminated subarachnoid bleeding.

Control Animals

In another group of animals designated operative controls, all procedures just described were performed with the exception of spinal cord compression.

Cerebrospinal Fluid Sampling

Samples of CSF were obtained from the lumbar subarachnoid space just before and after laminectomy (operative controls) or spinal cord injury (experimental group). Postoperative samples in both groups were obtained at 48-hour intervals starting at 24 hours and continuing for 17 to 21 days. All postoperative CSF samples were obtained with the animals lightly anesthetized with intramuscular ketamine hydrochloride (10 mg/kg). With the animals in a "sphinx-like" position and secured in a stereotaxic frame, the lumbar subarachnoid space was entered by percutaneous puncture with a short-beveled No. 20 needle between L-6 and L-7. The CSF samples were immediately centrifuged to remove any blood that might be present and refrigerated at 4° C until analyzed. It was determined that "slightly tinged" CSF samples (hematocrit of 2% or less) had no effect on CSF lactate or electrolyte levels if centrifuged immediately. Grossly bloody samples were discarded. All samples were analyzed within 48 hours for lactate, sodium (Na+), potassium (K+), calcium (Ca++), magnesium (Mg++), and
CSF lactate and electrolytes in cord injury

**Statistical Analysis**

All biochemical data obtained were statistically analyzed by the Mann-Whitney U test. Table 1 and Figs. 1 to 4 express the results as group means (as a summary statistic) together with the standard errors of the mean (SEM). A probability of 0.05 was used as the minimum level of significance.

**Results**

Lumbar CSF lactate, Na+, K+, Ca++, Mg++, and Cl− concentrations were determined at 48-hour time intervals for 17 to 21 days following either laminectomy and spinal cord compression (experimental) or laminectomy only (control).

Table 1 is a summary of the data appearing in Figs. 1 to 4 for both experimental and control animals. In addition, normal values (means ± SEM) for lactate and electrolytes have been included along with percentage changes from normal at each sampling interval for both control and experimental CSF lactate levels.

**Lactate Levels**

Data reported in Fig. 1 (solid line) and Table 1 reveal significant increases in CSF lactate levels on Days 1 through 9 post injury with peak levels (50% above normal) occurring at Day 5. In control animals (broken line), CSF lactate levels were significantly reduced by 24 hours post laminectomy and remained depressed throughout the 2- to 3-week experimental period. In these cats CSF lactate concentrations were reduced between 15% and 22% below normal (Table 1). There were significant differences between control and experimental CSF lactate concentrations at every sampling interval throughout the experiment.

**Electrolyte Levels**

There was no significant difference between control and experimental CSF Na+ levels at any sampling interval throughout the experimental period, although there was a tendency for Na+ to be elevated at 11 days post injury (Fig. 2, open squares; Table 1).
**TABLE 1**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Units</th>
<th>Group</th>
<th>Days Postop *</th>
<th>1</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>lactate</td>
<td>mg/100 ml</td>
<td>experimental</td>
<td>X = SEM</td>
<td>16.0 ± 1.1</td>
<td>17.9 ± 0.8</td>
</tr>
<tr>
<td>(normal values = 13.5 ± 0.4)</td>
<td>control</td>
<td>X = SEM</td>
<td>10.8 ± 0.8</td>
<td>10.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>sodium</td>
<td>mEq/l</td>
<td>experimental</td>
<td>X = SEM</td>
<td>155.8 ± 0.9</td>
<td>157.4 ± 0.7</td>
</tr>
<tr>
<td>(normal values = 157.1 ± 0.5)</td>
<td>control</td>
<td>X = SEM</td>
<td>157.8 ± 0.2</td>
<td>158.4 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>chloride</td>
<td>mEq/l</td>
<td>experimental</td>
<td>X = SEM</td>
<td>134.4 ± 1.0</td>
<td>137.2 ± 0.9</td>
</tr>
<tr>
<td>(normal values = 137.9 ± 0.3)</td>
<td>control</td>
<td>X = SEM</td>
<td>139.5 ± 0.6</td>
<td>137.0 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>potassium</td>
<td>mEq/l</td>
<td>experimental</td>
<td>X = SEM</td>
<td>2.8 ± 0.05</td>
<td>3.0 ± 0.05</td>
</tr>
<tr>
<td>(normal values = 2.8 ± 0.02)</td>
<td>control</td>
<td>X = SEM</td>
<td>2.8 ± 0.03</td>
<td>3.0 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>calcium</td>
<td>mEq/l</td>
<td>experimental</td>
<td>X = SEM</td>
<td>2.9 ± 0.04</td>
<td>3.2 ± 0.07</td>
</tr>
<tr>
<td>(normal values = 2.8 ± 0.04)</td>
<td>control</td>
<td>X = SEM</td>
<td>2.9 ± 0.09</td>
<td>2.9 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>magnesium</td>
<td>mEq/l</td>
<td>experimental</td>
<td>X = SEM</td>
<td>1.9 ± 0.04</td>
<td>1.9 ± 0.04</td>
</tr>
<tr>
<td>(normal values = 1.9 ± 0.02)</td>
<td>control</td>
<td>X = SEM</td>
<td>--</td>
<td>1.8 ± 0.0</td>
<td></td>
</tr>
</tbody>
</table>

*Includes both laminectomy plus injury (experimental) and laminectomy only (controls). All values are means (X) ± standard errors of the mean (SEM); N = number of animals.

Significant reduction at 24 hours was the only demonstrable change in CSF Cl− levels post injury (Fig. 2, open circles; Table 1).

Levels of CSF K+ were significantly elevated above normal on Days 3 through 13 post injury (Fig. 3, solid line; Table 1). However, CSF K+ concentrations from control animals were also significantly elevated on Days 3 through 7 (Fig. 3, broken line; Table 1) and the only significant difference between experimental and control CSF K+ levels occurred on Days 9 and 11.

Data reported in Fig. 4 (open squares, solid line) and Table 1 disclose a significant increase in CSF Ca++ levels on Days 3 through 13 post injury. Although control CSF Ca++ concentrations were slightly elevated on post-laminectomy Days 3 through 11, none of these increases were significant (Fig. 4, open
TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Days Postop*</th>
<th>5</th>
<th>7</th>
<th>9</th>
<th>11</th>
<th>13</th>
<th>15</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.1 ± 1.0</td>
<td>48.9</td>
<td>10.9 ± 0.5</td>
<td>157.7 ± 1.2</td>
<td>15.4 ± 0.8</td>
<td>13.5 ± 0.7</td>
<td>14.6 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>17.8 ± 1.0</td>
<td>31.9</td>
<td>11.0 ± 0.5</td>
<td>156.9 ± 1.0</td>
<td>16.5 ± 1.5</td>
<td>14.1</td>
<td>0</td>
<td>8.1</td>
</tr>
<tr>
<td>17.4 ± 1.2</td>
<td>28.9</td>
<td>10.6 ± 0.4</td>
<td>158.6 ± 1.0</td>
<td>22.2</td>
<td>14.8</td>
<td>-18.5</td>
<td>-16.3</td>
</tr>
<tr>
<td>16.5 ± 1.5</td>
<td>22.2</td>
<td>11.4 ± 0.3</td>
<td>160.6 ± 1.4</td>
<td>11.5 ± 0.3</td>
<td>11.0 ± 0.3</td>
<td>11.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>15.4 ± 0.8</td>
<td>14.1</td>
<td>11.5 ± 0.3</td>
<td>158.9 ± 1.1</td>
<td>11.0 ± 0.3</td>
<td>11.3 ± 0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.5 ± 0.7</td>
<td>0</td>
<td>11.0 ± 0.3</td>
<td>157.0 ± 1.1</td>
<td>11.3 ± 0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.6 ± 1.0</td>
<td>8.1</td>
<td>11.3 ± 0.2</td>
<td>158.0 ± 0.0</td>
<td>11.3 ± 0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant differences between experimental and control CSF Ca++ levels were noted on Days 3, 9, 11, 13, and 15 (Fig. 4 and Table 1).

Levels of CSF Mg++ were not significantly altered at any postinjury sample interval (Fig. 4, open triangles, solid line). However, variations in control CSF Mg++ levels (Fig. 4, open triangles, broken line) resulted in significant elevations of this ion on postlaminectomy Days 3 through 13. Consequently, significant differences between control and experimental CSF Mg++ levels occurred on Days 9 and 11 (Fig. 4 and Table 1).

**Discussion**

**Lactate Levels**

Our results demonstrated a significant rise in CSF concentrations of lactate by 24 hours postinjury.
post injury which remained elevated above normal values for 9 days. The average peak increase in CSF lactate levels occurred at 5 days post injury and thereafter declined toward normal. There is general agreement that: 1) there are considerable blood-brain and blood-CSF barriers to lactate; 2) CSF lactate finds its origin in nervous tissue and not in blood; and 3) CSF lactate levels reflect CNS extracellular fluid lactate levels. Therefore, the increases in CSF lactate seen in this study indicate a shift in injured spinal cord tissue metabolism toward anaerobiosis due to hypoxia. The prolonged elevation of CSF lactate suggests a continuing hypoxia of metabolically active spinal cord tissue for several days post injury. It has been reported that P02 levels decline in injured spinal cord tissue of experimental animals. In addition, a decrease in blood flow through central gray matter of traumatized spinal cord tissue has been demonstrated. Although not measured in our study, a decrease in blood flow through the injured area (with resulting hypoxia and perhaps also decreased "washout") is probably responsible for the elevated CSF lactate levels observed. The long-term elevation of CSF lactate is at variance with results reported by Locke, et al. After a 300-gm-cm impact injury in monkeys, they excised traumatized and non-traumatized (control) segments of spinal cord tissue at nine different time intervals (one monkey/time interval) ranging between 1.5 minutes and 48 hours post injury. These workers demonstrated elevated lactic acid concentrations in traumatized segments of spinal cord for 12 to 18 hours following injury, and concluded that the lactic acid increase presumably resulted from decreased oxygenation and perfusion. At 18 hours post injury, tissue lactate levels approximated control values. The reasons for the discrepancy between our data and those of Locke, et al. might include: 1) different methods of injury, that is, impact versus compression; 2) differences in the magnitude of injury; and 3) species differences. A slight delay between lactate release by hypoxic spinal cord tissue and its appearance in lumbar CSF may occur. This, however, could not account solely for the long-term (9-day) elevation in postinjury CSF lactate levels seen in our study.

It has been demonstrated that edema is a secondary posttraumatic complication of experimental spinal cord injury. Lewin, et al., found an increased tissue water content (edema) 1 day following impact spinal cord trauma in cats. Edema was maximum between Days 3 through 6 and had begun to decline by Day 9. Yashon, et al., reported evidence of edema 5 minutes after injury which persisted for 15 days reaching a maximum at 5 days following impact trauma to the spinal cord of monkeys. They concluded that since Locke, et al. found evidence of hypoxia (elevated tissue lactate levels) for only 18 hours post injury, long-term edema was due primarily to other factors. Our data imply that posttraumatic hypoxia of the spinal cord is of a long duration. Thus, the long-lasting edema reported by others may be dependent, at least in part, on hypoxia.

Taylor and Crockard indicate that serial CSF lactate levels can rise due to an expanding intracranial hematoma or increasing localized edema following head injury. Since the spinal cord is contained within the relatively inelastic pia mater, it has been proposed that the increased tissue volume raises the pressure on spinal cord tissue resulting in a secondary compression of parenchymal structures. Perhaps edema with resulting compression of spinal tissue vascular elements might contribute to the long-term hypoxia seen in this study. Further investigation of these questions is required before any definitive conclusions can be drawn.

The decrease in CSF lactate levels following laminectomy in the control animals was an unexpected, but consistent, finding. Several possibilities could explain this observation. These include: 1) a laminectomy-induced decrease in glucose utilization; 2) increase in oxygen extraction; or 3) increase in spinal cord tissue perfusion that increases "washout" and/or shifts tissue metabolism toward aerobiosis due to increased oxygen delivery to spinal cord tissue. Studies designed to determine which mechanisms are involved are currently in progress in our laboratory.

It is hoped that changes in CSF lactate levels will demonstrate a positive correlation with the degree of neurological deficit and return of neurological function in future animal studies and in human patients with spinal cord injuries. Lactate levels in CSF might then be of prognostic value and may
provide an index to the efficacy of various therapeutic modalities.

**Electrolyte Levels**

The only changes in CSF electrolyte composition that can be attributed to spinal cord trauma per se were significant elevations above levels in control animals of Ca\(^{++}\) concentrations on postinjury Days 3, 9, 11, 13, and 15, and in K\(^{+}\) concentrations on postinjury Days 9 and 11. Chloride levels in CSF were significantly reduced below those in control animals at 24 hours post injury. Changes in CSF electrolytes were minor, amounting to only a 0.2 to 0.3 mEq/l elevation for K\(^{+}\) and Ca\(^{++}\) and a 5 mEq/l decline for Cl\(^{-}\). It may be that the injured spinal cord segment was too small to be reflected in larger alterations of CSF electrolyte composition, especially after dilution within the CSF compartment. The presence of active clearance mechanisms for K\(^{+}\) from the subarachnoid space may have also played a role in keeping the concentration of this ion near normal values.\(^8\)

It is known that Ca\(^{++}\) binds to protein and increased Ca\(^{++}\) concentrations have been noted in CSF with elevated protein levels.\(^2\) While protein levels were not determined in all samples, periodic analysis revealed that CSF protein levels were slightly elevated above normal (60 to 75 mg/100 ml) at various intervals post trauma. The postinjury elevation of CSF Ca\(^{++}\) may, therefore, be a consequence of increased CSF protein levels.\(^3\)

Cerebrospinal fluid Cl\(^{-}\) levels can be secondarily decreased in the presence of increased CSF protein\(^3\) or HCO\(_3\)^{−}.\(^2\) Whether this is the basis for the decline in CSF Cl\(^{-}\) concentration at 24 hours post injury is unknown. Perhaps postinjury decline in CSF Cl\(^{-}\) was due to other unknown factors.

Potassium levels in CSF were significantly elevated above normal values on Days 3 through 13 post injury, as were the CSF K\(^{+}\) concentrations from control animals on Days 3 through 7 post laminectomy. The increase in CSF K\(^{+}\) values for the first postoperative week in both control and experimental animals may have been the result of non-specific tissue damage from repeated lumbar punctures. The only elevations in CSF K\(^{+}\) that might be attributed to the injury per se occurred on Days 9 through 11 post injury. Lewin, et al.,\(^13\) found a net loss of K\(^{+}\) from both injured and adjacent spinal cord segments 6 and 9 days following impact injury. They concluded that the K\(^{+}\) loss was due to necrotic as well as edematous changes in the injured cord. Thus, the significant CSF K\(^{+}\) elevations seen on Days 9 and 11 post injury are probably a reflection of this K\(^{+}\) loss from injured tissue.

Correlative histopathological findings in our laboratory are similar in many respects to those described in impact injury\(^5,7\) and suggest a common pathogenic mechanism. These findings include hemorrhagic necrosis of gray matter, microvacuolation and ischemic nerve cell change of anterior horn cells, “edematous” changes in white matter, and subsequent cavitation of the spinal cord involving gray and white matter with relative sparing of dorsal columns. These histological findings will be described in detail in a separate report.

**Acknowledgments**

The authors would like to thank Ms. Dianne Kikta, Gail Trocki, and Lisa Kalaf for their valuable technical assistance and also Ms. Robin Scott for typing the manuscript.

**References**


This work was supported in part by VA Project 0397-01.

Address reprint requests to: Douglas K. Anderson, Ph.D., Veterans Administration Hospital (151B), 13000 North 30th Street, Tampa, Florida 33612.