Abstract:
Cerebral Spinal Fluid Lactic Acid Following Circulatory Arrest

CSF lactic acid rises quickly and then gradually declines toward normal after severe cerebral ischemia in the dog. In animals in whom recovery can be postulated, the increase in lactic acid would appear to be transitory, and more severe insults produce higher levels. The increase in blood levels of lactic acid occurs more rapidly than that in the CSF, and the blood level returns to normal sooner than the CSF.

ADDITIONAL KEY WORDS: cerebral ischemia, brain lactate, tissue necrosis, brain death

Methods
Twenty-four large mongrel dogs were anesthetized with pentobarbital (30 mg per kg), intubated, and ventilated with ambient air utilizing a Harvard respirator. The region of the cisterna magna was exposed surgically, but the dura was left intact. The animals were monitored with intracranial EEG leads, placed with care to maintain an intact dura. During the entire procedure there was measurement of the arterial pressure, electrocardiograph (EKG) and EEG, and continuous recording of the CO₂ content of expired air. After a 20-minute period of recovery from cranial and thoracic surgery the superior and inferior vena cavae, plus aorta, were rapidly occluded for 2.5 to 10 minutes. CSF (0.3 cc) was obtained from the cisternal area before and at intervals during and after the ischemic insult. Although five minutes was the usual time of occlusion in these animals, two who manifested cardiac abnormalities were occluded for shorter periods of time. As per previous reports, EEG and pupillary changes, as well as continual arterial pressure recording, monitored the efficiency of aortic occlusion. Approximately 15 other dogs were submitted to longer periods of occlusion, but in most of these other manipulations also occurred, and they are not included in the data in table 1.

Results
As has been shown repeatedly with such total cerebral ischemia, the EEG becomes flat within 30 seconds, the pupils begin to dilate during the next 60 seconds, and the EEG remains flat so long as the animal is ischemic. In most animals within 20 minutes a significant return of EEG activity can be anticipated after five minutes of occlusion; after longer periods of occlusion the EEG may remain flat for over an hour.

The lactic acid in venous blood begins to rise slightly even while ischemia continues, but during ischemia CSF lactic acid increases only minimally and considerably less than brain lactate. The rise in CSF lactic acid occurs within five minutes after release of the aorta and cavae. Due to the limited quantity of CSF
in the dog, the number of samples is restricted; but it can be observed that within an hour following restoration of circulation, the CSF lactic acid starts to decline. There is a delay in the return of the CSF lactic acid to normal as compared to the drop in the blood level of lactic acid. A representative curve from one animal is presented in figure 1, and values are summarized in table 1. One animal that had two episodes of occlusion is presented in table 2.

Control values of blood lactic acid ranged from 0.7 to 2 meq/L, and values for CSF ranged from 0.9 to 2.2 meq/L. Five minutes after occlusion blood levels ranged from 1.1 to 6.5 meq/L, and CSF values varied from 1.6 to as high as 6.7 meq/L. In general, blood levels tended to be higher than CSF levels at five minutes after occlusion. Although initially after the ischemic insult the CSF values were lower, at 30 and 60 minutes the cerebral spinal fluid levels were higher than blood levels in almost all animals. Animals who had the longest period of ischemia, and those in whom the EEG remained flat throughout the entire experiment, invariably had the higher CSF lactic acid levels. CSF lactic acid values began to drop before 60 to 120 minutes in those animals that manifested a return of EEG activity.

As reported elsewhere, another five dogs which were subjected to shock with trimethaphan-camsylate (Arfonad) did not show as high an elevation of CSF lactic acid as of blood lactic acid. Hemorrhagic shock in five additional animals similarly failed to increase the CSF lactic acid to above 3 meq/L, even at 30 minutes after the insult. Nevertheless, in these animals blood levels ranged as high as 8 to 12 meq/L. In contrast in this experiment only three dogs who had had aortic occlusion failed to show a greater rise of lactic acid in the CSF than in blood, whereas the reverse was the case in all those with shock due to trimethaphan-camsylate or hemorrhage. Two of the three animals with aortic occlusion that demonstrated a higher blood level than CSF level of lactic acid had required cardiac massage to maintain the experiment.

**Comment**

This experiment confirms the hypothesis that after an episode of severe and total ischemia

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1**

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**Table 1**

<table>
<thead>
<tr>
<th>A. Results with Five-Minute Occlusion</th>
<th>Blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (24 animals)</td>
<td>0.69</td>
<td>1.7</td>
</tr>
<tr>
<td>5 min after clamp (18 animals)</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>30 min (18 animals)</td>
<td>3.4</td>
<td>4.6</td>
</tr>
<tr>
<td>60 min (14 animals)</td>
<td>1.9</td>
<td>3.8</td>
</tr>
</tbody>
</table>

B. CSF lactic acid compared with blood lactic acid

- Control — CSF lactic acid greater than blood value in 21 of 24
- 5 min — CSF lactic acid greater than blood in 50% of animals
- 30 min — CSF lactic acid greater than blood lactic acid in 13/18 of animals
- 60 min — CSF lactic acid greater than blood lactic acid in 13/14 of animals
CSF LACTIC ACID

TABLE 2
Animal with Two Episodes of Occlusion (First One Ten Minutes)

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>During ten-minute occlusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(at nine min)</td>
<td>3.3</td>
<td>2.0</td>
</tr>
<tr>
<td>(at five min)</td>
<td>3.1</td>
<td>7.4</td>
</tr>
<tr>
<td>(at 15 min)</td>
<td>1.3</td>
<td>6.5</td>
</tr>
<tr>
<td>(at 60 min)</td>
<td>1.1</td>
<td>5.4</td>
</tr>
<tr>
<td>During second clamping</td>
<td>1.6</td>
<td>5.2</td>
</tr>
<tr>
<td>five min after</td>
<td>4.1</td>
<td>6.7</td>
</tr>
<tr>
<td>30 min after</td>
<td>2.2 meq/L</td>
<td>11.0 meq/L</td>
</tr>
</tbody>
</table>

during which brain lactate rises the CSF lactic acid also rises. CSF is generally considered to be equivalent to extracellular fluid of the brain, and such a reflection in the CSF of the rise in brain lactate is not surprising. Patients who have had “brain death” may be expected to maintain the elevation in lactic acid for as long as the circulation and respiratory support is maintained and intracranial circulation is inadequate, and similar rises may occur when tissue damage is particularly severe.5 The very high elevated level of lactic acid in these patients is presumably related to the extensive nature of the injury. Most dogs that have sustained a five-minute period of ischemia can be expected to recover. As a rule EEGs were close to normal at the time of sacrifice in these animals.

It is not clear why hemorrhagic shock induced by the administration of trimethaphan-camsylate (Arfonad) produces a greater change in the lactic acid of systemic blood than in the levels of lactic acid in CSF. Total failure of cerebral perfusion during occlusion of the aorta may be a more severe cerebral insult than shock secondary to hemorrhage or drugs. In complete brain death endothelial thickening, clots in the microcirculation, and astrocytic swelling occur. It is possible that a lesser degree of total ischemia and circulatory stasis may produce similar, though milder, changes in the microcirculation, and thereby alter the permeability of these vessels to lactic acid.

Direct trauma and severe tissue necrosis would probably lead to a great excess of lactic acid and to a persistence of the abnormality, and could also explain the very high values found in patients with “brain death.” It is possible that in “brain death” the same mechanisms that led to necrosis and that perpetuate elevation in lactic acid also prevent adequate clearing of the lactic acid from the CSF.

Although the limited quantities of the CSF in the dog restricted the samples that can be obtained, the rise in lactic acid after a five-minute insult was shown to be transitory in these animals. More extensive or repeated insults in several animals (table 2) tended to increase the lactic acid level again. It was noted that vitreous humor rises similar to the spinal fluid, but from these and other studies the elevation of lactic acid in vitreous humor was not noted to be as predictable as are the changes in CSF.

An increase of lactic acid in CSF is, of course, not limited to necrosis or ischemia, since an increase in CSF lactic acid has been reported with meningitis as well as in hemorrhagic states. The CSF from all of these animals with the exception of two samples were all completely clear. In these two specimens a slight pinkish tinge was noted in one of the specimens obtained. In each the value was not increased.

In addition to CSF lactic acid, it would be of interest to check pyruvic acid levels as well, since both of these elements are invariably increased in the serum of animals or humans who have undergone irreversible shock.5 Nevertheless, levels of lactic acid and pyruvic acid change in a similar fashion in a setting of shock, and it is the lactic acid which changes the most remarkably. For these reasons, and because of simplicity of measurement, lactic acid from the CSF is considered more likely than pyruvate to be a useful clinical measure in “brain death.”

References

CORRECTION

The legends to figures 2 and 4 (page 442 and page 444) should be reversed.
Cerebral Spinal Fluid Lactic Acid Following Circulatory Arrest
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