Brain Lactate Metabolism in Humans With Subarachnoid Hemorrhage

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Background and Purpose—Lactate is central for the regulation of brain metabolism and is an alternative substrate to glucose after injury. Brain lactate metabolism in patients with subarachnoid hemorrhage has not been fully elucidated.

Methods—Thirty-one subarachnoid hemorrhage patients monitored with cerebral microdialysis (CMD) and brain oxygen (PbtO2) were studied. Samples with elevated CMD lactate (>4 mmol/L) were matched to PbtO2 and CMD pyruvate and categorized as hypoxic (PbtO2 <20 mm Hg) versus nonhypoxic and hyperglycolytic (CMD pyruvate >119 μmol/L) versus nonhyperglycolytic.

Results—Median per patient samples with elevated CMD lactate was 54% (interquartile range, 11%–80%). Lactate elevations were more often attributable to cerebral hyperglycolysis (78%; interquartile range, 5%–98%) than brain hypoxia (11%; interquartile range, 4%–75%). Mortality was associated with increased percentage of samples with elevated lactate and brain hypoxia (28% [interquartile range 9%–95%] in nonsurvivors versus 9% [interquartile range 3%–17%] in survivors; P=0.02) and lower percentage of elevated lactate and cerebral hyperglycolysis (13% [interquartile range, 1%–87%] versus 88% [interquartile range, 27%–99%]; P=0.07). Cerebral hyperglycolytic lactate production predicted good 6-month outcome (odds ratio for modified Rankin Scale score, 0–3 1.49; CI, 1.08–2.05; P=0.016), whereas increased lactate with brain hypoxia was associated with a reduced likelihood of good outcome (OR, 0.78; CI, 0.59–1.03; P=0.08).

Conclusions—Brain lactate is frequently elevated in subarachnoid hemorrhage patients, predominantly because of hyperglycolysis rather than hypoxia. A pattern of increased cerebral hyperglycolytic lactate was associated with good long-term recovery. Our data suggest that lactate may be used as an aerobic substrate by the injured human brain. (Stroke. 2012;43:1418-1421.)

Key Words: cerebral metabolism ■ brain hypoxia ■ hyperglycolysis ■ lactate ■ subarachnoid hemorrhage

L actate is central for the regulation of brain function. Produced via aerobic glycolysis by astrocytes, extracellular lactate is transferred to neurons, where it acts as an alternative substrate to glucose (astrocyte–neuron lactate shuttle).1,2 Generally considered a product of anaerobic metabolism, endogenous lactate is pivotal for neuronal survival,3,4 particularly in conditions of acute injury.5,6 Cerebral microdialysis (CMD) enables quantification of brain metabolites in cerebral extracellular fluid and provides information about energy metabolism and the extent of aerobic versus anaerobic glycolysis.7 Further insights can be obtained by combining CMD with brain oxygen (PbtO2) monitoring to quantify the extent of brain hypoxia.8

Brain lactate metabolism after subarachnoid hemorrhage (SAH) has not been fully elucidated. We hypothesized that elevations of brain lactate occur in poor-grade SAH patients either as the consequence of cerebral hyperglycolysis or as the consequence of brain hypoxia, and that differences in the patterns of elevated brain lactate may be associated with outcome.

Patients and Methods

We studied comatose patients with aneurysmal SAH admitted to the Division of Neurocritical Care, Hospital of the University of Pennsylvania, Philadelphia, and in the Department of Critical Care, Lausanne University Hospital, Switzerland, over a 4-year period and who underwent combined CMD–PbtO2 monitoring. Approval was obtained by local Institutional Review Board. Patients had at least 24 hours of valid intracranial monitoring and were alive for >5 days. Intracranial monitoring was performed as part of standard care, as previously described.9 Patients were managed according to a standard protocol in both centers;10 therapeutic targets were set to avoid cerebral perfusion pressure <60 mm Hg and PbtO2 <20 mm Hg.
CMD catheters (CMA 70; CMA Microdialysis AB; flow rate, 0.3 μL/min) and PbtO2 probes (Licox; Integra Neurosciences) were inserted via a triple-lumen bolt and placed into visually normal white matter. CMD samples were collected every 60 minutes and analyzed for concentrations of lactate, pyruvate, and glucose. Outcome at 6 months was assessed with the modified Rankin Scale score by 1 neurologist and 1 neurointensive care nurse who were blinded to physiological data.

First hour of monitored data, artifacts, and data points outside physiological ranges were excluded. Brain lactate elevations were defined as CMD lactate >4 mmol/L, based on recent studies. CMD samples were matched to PbtO2 values, averaged over the periods between CMD change times, and CMD pyruvate. Episodes with elevated brain lactate were categorized into 2 patterns, hypoxic (PbtO2 <20 mm Hg) versus nonhypoxic and hyperglycolytic (CMD pyruvate >119 μmol/L) versus nonhyperglycolytic, and expressed in percentage for each patient. For each time period analyzed, data analysis was performed using median per patient percentages of each pattern. Univariate analysis was used for comparisons using Mann-Whitney U or Fisher exact tests for data for a single time period and analysis of variance for repeated measures for data of different time periods (day 1–5). Logistic regression was used to examine associations between brain lactate metabolism and outcome: outcome (dichotomized as good-grade vs poor-grade SAH). Average “normal” values of CMD lactate in brain-injured patients are 2.699 ± 0.9 mmol/L. We used a cut-off of CMD lactate >4 mmol/L to define brain lactate elevation, in agreement with recent outcome studies. We found levels of brain extracellular lactate were frequently elevated during the early phase (1–5 days after injury) after SAH. Brain lactate elevations were predominantly related to cerebral hyperglycolysis rather than brain hypoxia. This suggests endogenous aerobic lactate release and supports the notion that lactate may be used as an alternative energy substrate by the injured human brain.

Lactate elevation per se may not be an unfavorable sign. We found that a pattern of hyperglycolytic lactate elevation was associated with good outcome, whereas hypoxic lactate elevations were associated with mortality and reduced likelihood of good recovery. Our findings are consistent with the existence of 2 sources of brain lactate: (1) increased glycolytic lactate secondary to aerobic metabolism, corresponding to satisfied energy needs and neuronal survival, ie, “good” lactate and (2) increased hypoxic lactate secondary to anaerobic metabolism, resulting from cell energy failure and neuronal loss, ie, “bad” lactate. These distinct brain metabolic patterns were associated with different patient outcomes.

The association of cerebral hyperglycolysis with outcome suggests this may be a compensatory response to avert energy failure. Recent animal experiments from our group show that administration of exogenous lactate exerts significant

### Table 1. Associations of Brain Lactate Metabolism With Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Value</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMD–lactate &gt;4 mmol/L</td>
<td>29 (8%–60%)</td>
<td>68 (59%–100%)</td>
<td>0.02</td>
<td>29 (11%–65%)</td>
<td>24 (2%–66%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypoxic</td>
<td>9 (3%–17%)</td>
<td>28 (9%–95%)</td>
<td>0.002</td>
<td>11 (4%–17%)</td>
<td>4 (1%–53%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hyperglycolytic</td>
<td>88 (27%–99%)</td>
<td>13 (1%–87%)</td>
<td>0.07</td>
<td>97 (87%–100%)</td>
<td>30 (10%–74%)</td>
<td>0.007</td>
</tr>
<tr>
<td>N of valid samples</td>
<td>158 (100–166)</td>
<td>100 (54–137)</td>
<td>0.06</td>
<td>155 (87–165)</td>
<td>153 (48–188)</td>
<td>0.89</td>
</tr>
<tr>
<td>Duration of brain monitoring, d</td>
<td>7 (7–7)</td>
<td>5 (4–7)</td>
<td>0.13</td>
<td>7 (7–7)</td>
<td>7 (6–7)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Data are medians (interquartile ranges).

CMD indicates cerebral microdialysis.

Discussion

This study aimed to investigate brain lactate metabolism in patients with poor-grade SAH. Average “normal” values of CMD lactate in brain-injured patients are 2.699 ± 0.9 mmol/L. Using logistic regression (Table 2), we found that a pattern of cerebral hyperglycolytic lactate predicted good recovery (OR, 1.49 for each 10% increase in cerebral hyperglycolytic lactate; CI, 1.08–2.05; P = 0.016), whereas a pattern of cerebral hypoxic lactate was associated with a reduced, albeit statistically nonsignificant, likelihood of good outcome (OR, 0.78 for each 10% increase in cerebral hypoxic lactate; CI, 0.59–1.03; P = 0.08).

**Results**

Thirty-one patients (mean age, 52 ± 10 years; 23 females) were studied and monitored a median of 1 day after injury for a median of 7 days (n = 3004 matched CMD/PbtO2 samples, of which 1424 had CMD lactate >4 mmol/L). Median per patient samples with CMD lactate >4 mmol/L was 54 (interquartile range, 11%–80%). Brain lactate elevations were more often attributable to cerebral hyperglycolysis (median per patient 78%; interquartile range, 5%–98%) than brain hypoxia (11%; interquartile range, 4%–75%). CMD lactate elevations were purely hypoxic in 8 patients (26%) and purely hyperglycolytic in 11 patients (35%), whereas 12 patients (39%) had both hypoxic and hyperglycolytic elevated lactate patterns observed.

Associations of brain lactate metabolism with 6-month outcome are shown in Table 1. Mortality was associated with an increased proportion of cerebral hypoxic lactate, whereas a pattern of elevated brain lactate and cerebral hyperglycolysis was associated with good recovery. Patterns over time (day 1–5) of elevated brain lactate for each outcome group are illustrated in the Figure. At all time points analyzed, brain hypoxic lactate production was higher among nonsurvivors than survivors (Figure A), whereas a pattern of cerebral hyperglycolytic lactate was associated with better long-term recovery (Figure B).

Using logistic regression (Table 2), we found that a pattern of cerebral hyperglycolytic lactate predicted good recovery (OR, 1.49 for each 10% increase in cerebral hyperglycolytic lactate; CI, 1.08–2.05; P = 0.016), whereas a pattern of cerebral hypoxic lactate was associated with a reduced, albeit statistically nonsignificant, likelihood of good outcome (OR, 0.78 for each 10% increase in cerebral hypoxic lactate; CI, 0.59–1.03; P = 0.08).
neuroprotection and that lactate transport is essential for long-term memory formation.14,15

Our study has several limitations. First, data are from a limited sample size, and thus need further validation by larger studies before they can be generalized. Second, global brain lactate metabolism was not assessed and we lack precise information regarding whether hypoxic lactate elevations were attributable to reduced cerebral blood flow or other factors. Finally, although elevated lactate may indicate increased flux, we cannot exclude that it may be related to reduced clearance in some cases.

SAH-related delayed neurological deterioration is a challenging problem involving different mechanisms and complex neuronal–glial interactions. Our study provides new insights into the role of endogenous brain lactate in humans with SAH. Our findings point to a novel link between brain lactate metabolism and SAH pathophysiology and outcome. Additional studies are warranted to further explore brain lactate metabolism in acute cerebral diseases and to investigate whether interventions aimed to modulate neuroenergetics are beneficial.

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Disclosures

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