Brain Lactate Metabolism in Humans With Subarachnoid Hemorrhage

Mauro Oddo, MD; Joshua M. Levine, MD; Suzanne Frangos, RN; Eileen Maloney-Wilensky, MSN; Emmanuel Carrera, MD; Roy T. Daniel, MD; Marc Levivier, MD; Pierre J. Magistretti, MD, PhD; Peter D. LeRoux, MD

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 (PbO2) were studied. Samples with elevated CMD lactate (>4 mmol/L) were matched to PbO2 and CMD pyruvate and categorized as hypoxic (PbO2 <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

Lactate 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 (PbO2) 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–PbO2 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 PbO2 <20 mm Hg.

Received December 20, 2011; accepted December 28, 2011.
From the Departments of Critical Care Medicine (M.O.) and Clinical Neurosciences (E.C., R.T.D., M.L.), Lausanne University Hospital, Lausanne, Switzerland; Laboratory of Neuroenergetics and Cellular Dynamics (P.J.M.), Brain Mind Institute, University of Lausanne, Lausanne, Switzerland; Departments of Neurosurgery (J.M.L., S.F., E.M.W., P.D.L.) and Neurology (J.M.L.), Hospital of the University of Pennsylvania, Philadelphia. Correspondence to Mauro Oddo, Department of Critical Care Medicine, Lausanne University Hospital, CH-1011 CHUV-Lausanne, Switzerland. E-mail mauro.oddo@chuv.ch
© 2012 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.111.648568

1418
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 Rankin Scale score 0–3 versus poor 4–6, including deaths, coded 6), coded 6, into poor 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 hyperglycolytic lactate 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 N = 19/31 (61%)</th>
<th>Nonsurvivors N = 12/31 (39%)</th>
<th>P Value</th>
<th>Good Outcome N = 12/19 (63%)</th>
<th>Poor Outcome N = 7/19 (37%)</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.
neuroprotection and that lactate transport is essential for long-term memory formation.\textsuperscript{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.

**Acknowledgments**

The authors thank Pedro Marques-Vidal, MD, MPH, for statistical consultation.

**Sources of Funding**

M.O. is supported by grants from the Swiss National Science Foundation (grant 320030\_138191) and the European Society of Intensive Care Medicine (ECCRN Clinical Research Award 2010).

**Disclosures**

E.M.W. and P.D.L. are members of Integra Lifesciences Speaker’s Bureau.

**References**


5. Cater HL, Chandrathena A, Benham CD, Morrison B III, Sandstrom LE. Lactate and glucose as energy substrates during, and after, oxygen de-
Brain Lactate Metabolism in Humans With Subarachnoid Hemorrhage
Mauro Oddo, Joshua M. Levine, Suzanne Frangos, Eileen Maloney-Wilensky, Emmanuel Carrera, Roy T. Daniel, Marc Levivier, Pierre J. Magistretti and Peter D. LeRoux

Stroke. 2012;43:1418-1421; originally published online February 16, 2012;
doi: 10.1161/STROKEAHA.111.648568

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/43/5/1418

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/