Patients with SAH are at great risk for brain energy failure as a consequence of the initial insult and focal and/or systemic complications. The aneurysm rupture commonly causes an increase in intracerebral pressure leading to a brief period of brain circulatory arrest. In the subacute phase, vasospasm and/or increased ICP develop in most patients with SAH, potentially reducing cerebral blood flow and impairing energy metabolism. The humoral systemic stress response can induce cardiac, hemodynamic, and respiratory complications that further augment the mismatch between brain energy supply and demand. Therefore, SAH treatment protocols focus on increasing blood volume, blood pressure, and CPP to maintain sufficient cerebral blood flow.

Increased ICP following SAH can be caused by clots, edema, ischemia, or reduced CSF absorption—individually or in various combinations. Intracranial pressure in the 15–20 mm Hg range is usually accepted in patients with SAH based on experience with TBI patients. However, the rationale behind this somewhat arbitrary ICP threshold in SAH is seldom discussed and has not been

Relationship between intracranial hemodynamics and microdialysis markers of energy metabolism and glutamate-glutamine turnover in patients with subarachnoid hemorrhage

Clinical article

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**Object.** The aim of this study was to explore the relationship between hemodynamics (intracranial and systemic) and brain tissue energy metabolism, and between hemodynamics and glutamate (Glt)-glutamine (Gln) cycle activity.

**Methods.** Brain interstitial levels of lactate, pyruvate, Glt, and Gln were prospectively monitored in the neurointensive care unit for more than 3600 hours using intracerebral microdialysis in 33 patients with subarachnoid hemorrhage (SAH). Intracranial pressure (ICP), mean arterial blood pressure, and cerebral perfusion pressure (CPP) were recorded using a digitalized system.

**Results.** Intestinal Gln and pyruvate correlated with CPP (r = 0.25 and 0.24, respectively). Intracranial pressure negatively correlated with Gln (r = –0.29) and the Gln/Glt ratio (r = –0.40). Levels of Gln and pyruvate and the Gln/Glt ratio were higher and levels of Glt and lactate and the lactate/pyruvate ratio were lower during periods of decreased ICP (≤ 10 mm Hg) as compared with values in periods of elevated ICP (> 10 mm Hg). In 3 patients, a poor clinical condition was attributed to high ICP levels (range 15–25 mm Hg). When CSF drainage was increased and the ICP was lowered to 10 mm Hg, there was an instantaneous sharp increase in intestinal Glt and pyruvate in these 3 patients.

**Conclusions.** Increasing interstitial Gln and pyruvate levels appear to be favorable signs associated with improved CPP and low ICP. The authors suggest that this pattern indicates an energy metabolic situation allowing augmented astrocytic energy metabolism with accelerated Glt uptake and Gln synthesis. Moreover, their data raised the question of whether patients with SAH and moderately elevated ICP (15–20 mm Hg) would benefit from CSF drainage at lower pressure levels than what is usually indicated in current clinical protocols.

**Key Words** • intracranial pressure • glutamate • glutamine • lactate • microdialysis • pyruvate

Abbreviations used in this paper: CPP = cerebral perfusion pressure; FHP = fulminant hepatic failure; Gln = glutamine; Glt = glutamate; HPLC = high performance liquid chromatography; ICP = intracranial pressure; L/P = lactate/pyruvate; MABP = mean arterial blood pressure; NICU = neurointensive care unit; SAH = subarachnoid hemorrhage; VD = ventricular drain.

See the corresponding editorial in this issue, pp 907–909.
extensively studied. Heuer et al.2 have reported that an ICP > 20 mm Hg is common after SAH and correlates with a worse outcome; but because ICP varied with SAH severity, it did not independently predict outcome. Ryttle -fors et al.11 have recently shown that periods with ICPs > 20 mm Hg following SAH are associated with clinical deterioration, whereas periods with CPPs > 100 mm Hg are associated with clinical improvement. However, even an ICP of 15 mm Hg is above normal and can impair the brain microcirculation, especially during vasospasm.18 When accepting ICP levels between 15–20 mm Hg, we may subject an already vulnerable brain to additional stress. One argument in favor of allowing relatively high ICP in patients with SAH is that aggressive CSF drainage can induce aneurysm rupture and/or worsen the consequences of a rebleeding—even though the aneurysm is repaired, the risk of a rebleed is eliminated.

Approximately 80% of the brain’s energy metabolism is normally used for cycling Glu and Gln between neurones and astrocytes.15 Interstitial Glu levels are kept low thanks to efficient uptake into astrocytes where Glu is converted to Gln. Glutamine is released back to the interstitial compartment where it is taken up by neurones and reconverted to Glu. Ischemia is associated with high interstitial Glu levels, which are believed to contribute to secondary damage and brain cell death.29 Using intracerebral microdialysis in patients with SAH, we recently studied interstitial Glu and Gln levels in relation to ischemia, defined as increased lactate/pyruvate (L/P) ratios. Besides confirming a strong correlation between the L/P ratio and Glu, we found that brain interstitial Gln levels correlate with interstitial pyruvate levels,13 suggesting that low pyruvate levels are accompanied by reduced Glu-Gln cycle activity. Increasing interstitial pyruvate levels have been associated with good recovery in patients with SAH1 and may be a sign of improving glycolytic activity.

In the present study we wanted to explore the possible relationship among brain energy metabolism, the Glu-Gln cycle activity, and intracranial hemodynamics. Therefore, brain interstitial lactate, pyruvate, L/P ratio, Glu, Gln, and Gln/Glu ratio as well as ICP, CPP, and MABP were prospectively recorded in patients with spontaneous SAH.

Methods

The local ethics committee for human research approved this study. Informed consent to participate was obtained from all patients or their proxy.

Patient Population

Thirty-three patients—22 women and 11 men—with spontaneous SAH who had been admitted to the NICU at Uppsala University Hospital between April 2003 and September 2005 and who had undergone microdialysis monitoring were included in the study. The mean (± SD) patient age was 55.5 ± 8.9 years. The median World Federation of Neurosurgical Societies SAH grade6 was III (range I–V). The aneurysms were treated surgically (16 patients) or with endovascular therapy (16 patients). In 1 patient no aneurysm was found. Either before or during treatment of the aneurysm, a microdialysis probe was placed in the frontal (30 patients) or temporal (3 patients) lobe cortex via a separate bur hole adjacent to a VD (28 patients) or through a bone flap (5 patients). Care was taken to insert the probe in what appeared to be uninjured cortex. The mean period from the first sign of SAH to the start of microdialysis sampling was 29.5 ± 24 hours, and the mean duration of sampling was 112 ± 37 hours. In our neurointensive care protocol, all patients with SAH follow a regimen of bed rest and nimodipine; the aim is to keep the patients normovolemic and normotensive. Patients with a decreased level of consciousness are intubated and receive ventilation to maintain normocapnia. All intubated patients are sedated with propofol and bolus doses of morphine. Muscle relaxants are used only during the intubation procedure. All patients had a VD for ICP monitoring and CSF drainage. We aim to keep ICP below 20 mm Hg and usually initiate CSF drainage at 15 mm Hg.

Since 1998 a networked, computerized multimodality monitoring system connected to a central server has been used to collect and store physiological data obtained in the Uppsala NICU.3 One value per minute is displayed and saved for each channel and patient. Data collection is sometimes interrupted during radiological examinations or when a patient is taken to the operating theater. The data were manually validated, and the software was used to identify extreme values.3 Negative ICP values were either removed or set to 0.

Microdialysis Monitoring

Intracerebral microdialysis was performed using CMA 70 probes with a 10-mm membrane length (CMA Microdialysis). The probes were perfused with artificial CSF (Na+ 148 mmol/L, Ca2+ 1.2 mmol/L, Mg2+ 0.9 mmol/L, K+ 2.7 mmol/L, and Cl− 155 mmol/L) at a rate of 0.3 μl/minute by using a CMA 106 microinjection pump (CMA Microdialysis). Samples were taken hourly and analyzed at bedside for lactate, pyruvate, and urea with enzymatic techniques using a CMA 600 microdialysis analyzer (CMA Microdialysis). Urea was monitored to control the probe performance.6 At least 3 hours passed between the insertion of the probe and the onset of sampling to allow for normalization of changes due to probe insertion. Quality controls at 2 different concentrations for each substance were performed every weekday. Imprecision values for between-assay coefficient of variation was <10% for the low-concentration control sample and <5% for the high-concentration control sample. Samples were analyzed for Glu and Gln using HPLC with fluorescence detection, as described in detail elsewhere.2 Briefly, the amino acids were automatically derivatized with o-phthaldialdehyde in a CMA 200 refrigerated microSampler (CMA Microdialysis) and gradient-separated on a Nucleosil C18 column 5 μm (60 × 4 mm, CMA Microdialysis). The mobile phase gradient consisted of 0.1 mol/L sodium acetate buffer, pH 6.7, with 2.5% tetrahydrofuran and methanol concentration increasing from 5 to 97.5%. Quality control measurements on the HPLC system were performed daily using blank water samples as well as standardized calibration solutions mimicking those of the human samples. In addition, internal control
samples were run together with each patient series. Imprecision values were 3–5% for the within-assay coefficient of variation and 5–9% for the between-assay coefficient of variation for the Glt and Gln measurements. Each hourly microdialysis sample was stamped with the time of collection. Because of dead space in the microdialysis tubing, which corresponded to a lag phase of 17 minutes, the dialysis fluid in a sample reflected the brain interstitial milieu during the period 17–77 minutes before the stamped collection time.

Recording the Clinical Course

Patient charts were retrospectively studied for information regarding the level of consciousness, level and volume of CSF drainage, fever episodes, cardiopulmonary problems, surgical procedures, extubations, and radiological examinations.

Statistical Analysis and Presentation of Data

Statistical analysis and graphical presentation were performed using Statistica, version 7.1. for Windows (StatSoft, Inc.). Results were regarded as significant if p < 0.05.

Each hourly microdialysis sample measurement was matched to the mean ICP, MABP, and CPP during the hour when the sample was collected. Parametric (Pearson linear) correlation analyses were performed to study the relationship between microdialysis data and pressure data. Correlation coefficients > 0.20 were considered to be of potential significance.

Microdialysis data were grouped depending on whether ICP was normal (≤ 10 mm Hg) or elevated (> 10 mm Hg). The 2 groups were compared and described using parametric and nonparametric statistics.

Results

In total, 3617 hours in the NICU were monitored using microdialysis and the computerized multimodality monitoring system. The ICP distribution during observation is presented in Fig. 1. Cerebral perfusion pressure was positively correlated with Gln (r = 0.25; Fig. 2A) and pyruvate (r = 0.24; Fig. 2B). Pyruvate was positively correlated with MABP (r = 0.23). Glutamine and the Gln/Glt ratio were negatively correlated with ICP (r = −0.29 and −0.40; Fig. 2C).
Three of the 33 patients experienced high mean hourly ICPs in the 15–25 mm Hg range, and their clinical deterioration or lack of improvement was attributed to hydrocephalus and/or high ICP of another origin. None of them had severely pathological microdialysis patterns during the period when ICP was high; the L/P ratios were < 30 and Glt levels were < 15 μM. As a consequence of the high ICP, the VD was opened at 10 mm Hg in these 3 patients. Opening the drain and lowering the mean hourly ICP to 10 mm Hg were, in all cases, associated with interstitial Gln and pyruvate surges, which are illustrated in Fig. 3.

Glutamine, Gln/Glt ratio, and pyruvate were significantly higher and Glt, lactate, and L/P ratio were significantly lower during ICP periods ≤ 10 mm Hg as compared with periods > 10 mm Hg (p < 0.05; Table 1).

Discussion

We have recently reported that brain interstitial Glt increases and interstitial Gln decreases during periods of energy failure, defined as L/P ratios > 40 with low pyruvate levels, suggesting reduced Glt-Gln cycling due to a limited energy producing capacity. During periods of high energy demand when there is increased glycolysis, defined as high interstitial lactate and pyruvate levels, interstitial Gln levels increase, which may indicate accelerated astrocytic Glt-Gln cycle activity in response to increased interstitial Glt levels. In the present study, we focused on the relationship between systemic pressure and ICP parameters and microdialysis variables related to energy metabolism and Glt turnover, following SAH. To our knowledge, this relationship has not been studied.

Glutamine and pyruvate were positively correlated with CPP. These variables increased over time and during the stay in the NICU. It is possible that increasing interstitial concentrations of pyruvate and Gln, which were observed in the majority of patients, are a direct consequence of improved cerebral perfusion. The linear relationship among CPP, MABP, and pyruvate support...
mean Glt levels and L/P ratios as compared with patients with SAH who experience ICP > 20 mm Hg have higher tissue energy metabolism. It has been shown that patients IC P . The 3 cases illustrated that a moderately increased which in these 3 cases appeared to be an unfavorably high energy metabolic boost on the alleviation of a constraint, We interpreted this microdialysis pattern as a sign of an followed by a surge in interstitial Gln and pyruvate levels. The VD at 10 mm Hg (Fig. 3). Lowering of the ICP was increased and ICP was lowered by opening could be directly observed in 3 patients in whom CSF drainage was increased and ICP was lowered by opening the VD at 10 mm Hg (Fig. 3). Lowering of the ICP was followed by a surge in interstitial Gln and pyruvate levels. We interpreted this microdialysis pattern as a sign of an energy metabolic boost on the alleviation of a constraint, which in these 3 cases appeared to be an unfavorably high ICP. The 3 cases illustrated that a moderately increased mean hourly ICP (15–25 mm Hg) appears to hamper brain tissue energy metabolism. It has been shown that patients with SAH who experience ICP > 20 mm Hg have higher mean Glt levels and L/P ratios as compared with patients without high ICP periods, and that high ICP (> 20 mm Hg) periods are associated with clinical deterioration following SAH. Data in the present study made us question whether patients with SAH and moderately elevated ICP (15–20 mm Hg) would benefit from CSF drainage at a lower pressure level than that stated in current clinical treatment protocols. The consistent pattern of pyruvate and Gln increases after lowering of the ICP also vividly illustrated the utility of microdialysis as a method for assessing treatment effects at the brain tissue level.

Brain interstitial Glt has been extensively studied, but data on normal human brain interstitial Gln levels are scarce. In pediatric patients with traumatic brain injury and adult NICU patients in whom microdialysis setups similar to ours have been used, the highest Gln level was 572 and 1200 μM, respectively. In animals, basal brain interstitial Gln concentrations have ranged between 150 and 1000 μM. In view of these findings it appears that Gln levels > 1000 μM, which were present in a proportion of our cases (Fig. 2A and C), are elevated. In patients with FHP, increased brain Gln synthesis may play a role in brain edema formation by increasing the brain water content and ICP. In patients with FHP who experienced ICP levels above 20 mm Hg, brain interstitial Gln levels ranged from 700 to 10,000 μM (mean 6500 μM) when using a microdialysis setup similar to ours. Interestingly, the lower Gln levels in that cohort overlapped with the higher Gln levels in our cohort with SAH. However, in FHP there was a positive correlation between Gln levels and ICP, whereas the correlation between ICP and Gln was negative in SAH.

We have characterized data from our patient cohort with respect to the interrelationship between various microdialysis variables; it was found that brain interstitial Gln correlates with pyruvate and that Gln levels increase during the NICU stay in most patients. We have also observed surges in Gln and pyruvate following normalization of ischemic microdialysis patterns (high L/P ratio and high Glt) and during delayed ischemic neurological deteriorations. In the present study, we reported on the occurrence of Gln surges and increasing pyruvate levels following the active lowering of ICP. Increasing Gln and pyruvate levels may be a favorable response in metabolically challenged tissue in which astrocytes try to maximize their glycolytic rate to yield adenosine 5′-triphosphate for the energy-demanding uptake of Glt.

### Conclusions

In this prospective observational NICU study, microdialysis data, ICP, CPP, and MABP were monitored during more than 3600 hours in 33 patients with SAH. The results showed that Gln and pyruvate levels correlate with CPP. Pyruvate correlates with MABP. Glutamine and the Gln/Glt ratio negatively correlate with ICP. According to collected microdialysis data, some patients appear to experience disturbed cerebral metabolism due to increased ICP at levels below the usual treatment thresholds. Periods with an ICP > 10 mm Hg were associated with a significantly worse microdialysis pattern, including lower Gln/Glt ratios and higher L/P ratios. Interstitial surges in Gln and pyruvate appeared in all cases in which a high ICP was treated with CSF drainage at 10 mm Hg.

We submit that alterations in the interstitial levels of Gln and pyruvate partly reflect the astrocytic metabolic activity. Increasing interstitial Gln and pyruvate levels af-

### Table 1: Mean and median cerebral interstitial metabolite concentrations in 33 patients with SAH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ICP &gt;10 mm Hg</th>
<th>ICP ≤10 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>2723</td>
<td>780</td>
</tr>
<tr>
<td>Glt (µM) mean</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>median</td>
<td>5.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Gln (µM) mean</td>
<td>567</td>
<td>748</td>
</tr>
<tr>
<td>median</td>
<td>499</td>
<td>686</td>
</tr>
<tr>
<td>Gln/Glt mean</td>
<td>128</td>
<td>382</td>
</tr>
<tr>
<td>median</td>
<td>86</td>
<td>228</td>
</tr>
<tr>
<td>lactate (µM) mean</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>median</td>
<td>3.3</td>
<td>2.9</td>
</tr>
<tr>
<td>pyruvate (µM) mean</td>
<td>143</td>
<td>148</td>
</tr>
<tr>
<td>median</td>
<td>130</td>
<td>147</td>
</tr>
<tr>
<td>L/P mean</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>median</td>
<td>24</td>
<td>21</td>
</tr>
</tbody>
</table>

* For all metabolites the difference between the groups was statistically significant (p < 0.01).
ter a period of high ICP and/or low CPP appear to be a sign of a favorable energy metabolic situation allowing augmented astrocytic metabolism with accelerated Glt uptake and Gln synthesis. Finally, our findings support clinical treatment protocols targeting high CPP and low ICP in patients with SAH.

Disclosure

Financial support for this study was obtained from the following contributors: Swedish Medical Research Council, Grant Nos. 521-2004-6210 and 521-2007-3254 (L.H.); GlaxoSmithKline (C.S.); the Margarethahemmet Foundation (C.S.); the Erland Wessler Foundation (C.S.); the Ahlén Foundation (L.H.); the Selanders Foundation (C.S.); and Uppsala University Hospital (C.S., T.H., E.K., P.E., L.H., and E.R.E.).

Acknowledgments

The authors are grateful to Inger Ståhl-Myllyahmo, for her expertise with the HPLC system, and to the staff in the neurointensive care unit, for their care of the patients and collection of the microdialysis samples.

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