Editorial

Subarachnoid hemorrhage and microdialysis

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Aneurysmal subarachnoid hemorrhage (SAH) affects 10 per 100,000 people each year, and the outcome is poor. Many patients die immediately, and among those who reach the hospital alive, 25% die and ~ 50% of the survivors remain disabled. Death and disability are usually attributed to brain damage from the initial effects of the hemorrhage and delayed complications such as delayed cerebral ischemia usually due to vasospasm. Given the major impact of the initial hemorrhage, a better understanding of it would be important for improving the overall outcome, although little has been achieved in that regard. Rebleeding as a cause of poor outcome has been declining in importance with the advent of routine early aneurysm obliteration and perhaps short courses of anti-fibrinolytic drugs if early obliteration cannot be done. Thus, we tend to focus on preventing secondary brain injury and treating delayed cerebral ischemia. In the following paper by Samuelsson and colleagues, the authors have used microdialysis to gain a better understanding of the possible mechanisms of brain injury after SAH.

Microdialysis uses a small probe with a semipermeable membrane that is inserted into the brain. The probe is perfused with electrolyte solution, and molecules in the extracellular space around the probe diffuse across the membrane into an electrolyte solution, which is collected and measured. The molecule must be water-soluble and have a molecular weight below the cutoff weight of the membrane. Absolute concentrations cannot be measured, but relative values over time can be obtained. Cerebral ischemia has been studied widely and is believed to be indicated by decreased glucose and pyruvate and increased lactate, glycerol, and glutamate. The ratios of lactate/pyruvate (L/P) and glutamate (Glt)/glutamine (Gln) also increase. Most of the prior studies in patients with SAH have been focused on demonstrating that these changes seem to relate to cerebral ischemia and on whether they can be used to predict the development of ischemia.

The Samuelsson et al. study is a further analysis of their series of 33 patients with SAH who were monitored for an average of ~ 109 hours each, for a total of 3600 hours. They inserted microdialysis probes and began measurements ~ 30 hours after SAH and continued them for ~ 4.5 days. Lactate, pyruvate, Glt, and Gln were measured. Their new findings are that decreasing cerebral perfusion pressure (CPP) is associated with decreasing Gln and pyruvate, increasing Glt, and a decreasing Gln/Glt ratio. High intracranial pressure (ICP) also was associated with increased lactate, Glt, L/P ratio, and Glt/Gln ratio. In general, the lower the CPP, the worse the brain metabolism, which means a higher lactate level, lower pyruvate level, and higher L/P ratio. The Glt/Gln ratio also increases as CPP decreases. I am making the assumption that these parameters are bad for the brain or indicate that something detrimental is occurring.

Samuelsson and colleagues describe 3 patients with episodes of increased ICP that were associated with clinical deterioration. Lowering the ICP was associated with increased Gln and pyruvate, although the increase in pyruvate looks lower in 1 of the patients. Inspection of the figures suggests that CPP was maintained above 70 mm Hg. Patient outcome is not described; whether lowering the ICP reversed the deterioration and improved outcome as opposed to what would have happened otherwise would be of interest. First, I wonder whether the deterioration was caused by increased ICP or whether something else caused the deterioration and the alteration in biochemistry with the ICP increased by brain swelling or some other mechanism. Second, what was the CPP during these episodes? Third, we need to know how many similar surges in Gln and pyruvate occurred in the absence of changes in ICP and/or CPP, and how many acute increases or decreases in ICP and/or CPP occurred without the biochemical changes? Knowing the frequency of these events would provide the comparison groups from which to determine if the increases in Gln and pyruvate and reductions in ICP are even associated rather than just coincidental. In their prior analysis, Samuelsson et al. identified 13 episodes of “energy crisis” indicated by an L/P ratio > 40 in the 33 patients. The hemodynamics during these episodes must be analyzed.

The key point the authors make is that lowering the ICP to maintain adequate or high levels of pyruvate and Gln may be beneficial, and that these biochemical effects may occur with lower ICPs (that is, < 15–20 mm Hg) than are sometimes recommended. This provocative recommendation contrasts with some management schemes. For example, one method of managing increased ICP is CPP-guided: one tries to keep the CPP > 60 or 70 mm Hg without specifically addressing the increased ICP. Another example is when after SAH, I sometimes do not use ventricular drainage in patients with good clinical grades who undergo surgery when the brain is slack and brain retraction is not needed. In patients who undergo endo-
vascular treatment of a ruptured aneurysm, ventricular drainage is usually used only in patients with poor clinical grades. This finding is based in part on the unproven assumption that forcing normal intracranial circulation of CSF out of the ventricles and through the subarachnoid space promotes clot clearance and decreases the delayed detrimental effects of SAH on the brain. The ICP can be high in these patients. But there is emerging evidence to support the contention of Samuelsson and colleagues that this may not create the best milieu for the brain. For example, Dunham, et al.² found evidence of cerebral hypoxia at some times in patients with head injuries even when CPP was > 70 mm Hg.

Some assumptions and limitations still must be addressed with further research before we fully understand these data and adopt the recommendations. Microdialysis samples only a small area of the brain. The findings in this study are only correlations of biochemical measurements and CPP. Their statistical methods also could have been conducted another way. The authors assumed that each measurement (3617 hours or measurements in 33 patients or ~ 109 measurements per patient) was independent, whereas they had multiple measurements (~ 109) in 33 patients. This approach is different and is usually handled differently statistically. The authors report a trend in which Gln and pyruvate tend to increase over time; this trend should be taken into account when analyzing the data.

In summary, the authors have a substantial database of microdialysis monitoring in patients with SAH from which they will be able to generate some interesting hypotheses. The current analysis suggests that increased ICP, perhaps independent of reduced CPP, impairs brain metabolism. If this hypothesis can be confirmed in larger numbers of patients and treatment can be undertaken with improved outcome, then a major advance will have been made.

References

Response
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We appreciate the editorial comments. Maintaining an adequate cerebral energy metabolic capacity is of major importance in neurointensive care. Events resulting in failing substrate delivery or increasing metabolic demands are known as secondary insults and can lead to energy failure and a worse outcome. Patients with aneurysmal SAH appear to be sensitive to such secondary disturbances, probably because most of these patients experienced transient global brain ischemia at the time of aneurysm rupture.

From animal studies, it is known that a major part of the brain’s energy consumption is connected to the Glu-Gln cycle. Therefore, an interesting question arose: was there a possible relationship between signs of disturbed cerebral energy metabolism and the interstitial levels of Glu and Gln as measured with intracerebral microdialysis in patients with SAH?

When analyzing our material we used 3 different approaches. First, we used microdialysis criteria to define ischemia as periods in which the L/P ratio reached above 40. We found that periods with an L/P ratio > 40 and low pyruvate levels were associated with decreased interstitial Glu levels, suggesting a disturbed energy producing capacity leading to failing astrocytic Glu uptake and low Glu synthesis. Conversely, periods with an L/P ratio > 40 with normal or high pyruvate levels were associated with increased interstitial Glu levels, which may represent a more favorable metabolic situation with maintained astrocytic Glu uptake and intense Glu synthesis. Thus, it seems that moderately elevated L/P ratios cannot always be interpreted as failing energy metabolism. In cases of high L/P ratio, pyruvate and/or Gln levels may determine whether or not there is sufficient energy for Glu-Gln cycling. We found this notion particularly interesting in the context of the emerging concept of relative glucose deficiency due to competition among the energy-consuming pathways recently observed in brain-injured patients.³

Intracranial pressure and CPP levels are carefully