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Clinical Neurochemistry of Subarachnoid Hemorrhage: Toward Predicting Individual Outcomes via Biomarkers of Brain Energy Metabolism

Yannick Tholance,[*,†,‡] Gleicy Barcelos,[§] Frederic Dailler,[∥] Armand Perret-Liaudet,[⊥,#] and Bernard Renaud[*,⊥,▽]

[†]EA 6309 - Myelin Maintenance and Peripheral Neuropathies, University of Limoges, 2 rue du Dr Marcland, 87025 Limoges, France

[‡]Department of Biochemistry and Molecular Genetics, CHU Dupuytren, 2 av Martin Luther King, 87042 Limoges, France

[§]Department of Anesthesiology, Pharmacology and Intensive Care, Geneva University Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva, Switzerland

[∥]Neuro-intensive-care Unit, Neurological Hospital, and [⊥]Laboratory of Neurobiology, Neurochemistry Unit, Department of Biochemistry and Molecular Biology, Hospices Civils de Lyon, 59 bd Pinel, 69677 Bron, France

[#]BioRaN Team, Lyon Neuroscience Research Center, CNRS, UMR 5292, INSERM U1028, Lyon-1 University, 59 bd Pinel, 69677 Bron, France

[▽]Neurodialytics Unit, Lyon Neuroscience Research Center, CNRS, UMR 5292, INSERM U1028, Lyon-1 University, 8 Avenue Rockefeller, 69008 Lyon, France

ABSTRACT: The functional outcome of patients with subarachnoid hemorrhage is difficult to predict at the individual level. The monitoring of brain energy metabolism has proven to be useful in improving the pathophysiological understanding of subarachnoid hemorrhage. Nonetheless, brain energy monitoring has not yet clearly been included in official guidelines for the management of subarachnoid hemorrhage patients, likely because previous studies compared only biological data between two groups of patients (unfavorable vs favorable outcomes) and did not determine decision thresholds that could be useful in clinical practice. Therefore, this Viewpoint discusses recent findings suggesting that monitoring biomarkers of brain energy metabolism at the level of individuals can be used to predict the outcomes of subarachnoid hemorrhage patients. Indeed, by taking into account specific neurochemical patterns obtained by local or global monitoring of brain energy metabolism, it may become possible to predict routinely, and with sufficient sensitivity and specificity, the individual outcomes of subarachnoid hemorrhage patients. Moreover, combining both local and global monitoring improves the overall performance of individual outcome prediction. Such a combined neurochemical monitoring approach may become, after prospective clinical validation, an important component in the management of subarachnoid hemorrhage patients to adapt individualized therapeutic interventions.

KEYWORDS: *Cerebral microdialysis, retrograde jugular catheterization, metabolic ratio, elevated hypoxic lactate, metabolic crisis, functional outcome, subarachnoid hemorrhage, delayed cerebral ischemia*

Subarachnoid hemorrhage is a serious, life-threatening type of stroke that is characterized by bleeding into the meningeal subarachnoid space surrounding the brain. Subarachnoid hemorrhage originates, in most cases, from an aneurysmal rupture. While this type of brain cerebrovascular event represents only 5% of all strokes, it tends to affect younger people (median age of 50 years) compared to other types of stroke. Moreover, subarachnoid hemorrhage is associated with high morbidity/mortality rates despite progress in its management. Therapeutic intervention includes terminating primary bleeding, avoiding further bleeding events by surgical or endovascular occlusion of the aneurysm, restoring normal regional blood flow, reducing intracranial pressure, and preventing delayed complications. The latter include delayed cerebral ischemia, which represents the major cause of morbidity and mortality after the initial stroke event. Delayed cerebral ischemia occurs in approximately 30% of patients and is generally due to cerebral vasospasm.

Initial neurological status after subarachnoid hemorrhage is evaluated by clinical rating scales such as the Glasgow or World Federation of Neurological Surgeons (WFNS) scales, and/or by radiological assessment of bleeding severity (Fischer scale). Poor long-term functional outcome is predicted when initial evaluation in the neuro-intensive care unit (NICU) indicates a poor clinical grade (grades IV and V of the WFNS scale, e.g.) and an extensive subarachnoid hemorrhage on a cerebral computed tomography scan (grades III and IV of the Fischer scale). Nonetheless, these initial evaluations are of limited value for predicting long-term outcome in the case of delayed complications. For example, it is not uncommon that some patients with a positive initial clinical status have a long-term unfavorable outcome that includes severe disability, likely due to cerebral infarct following the occurrence of undetected delayed cerebral ischemia. By contrast, some patients with poor initial

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clinical status recover over time with an unexpected and rather favorable long-term outcome.

Thus, detection of delayed cerebral ischemia appears to be of critical importance and requires extensive clinical monitoring in the NICU. This secondary outcome is characterized by sudden neurological deterioration. In such cases, a rapid adaptation of pharmacological treatment and/or of the patient's general management is needed to improve the long-term functional outcome. Clinical monitoring is very limited for patients who are in a coma, a condition that is frequent in subarachnoid hemorrhage patients who have poor-grade status at admission (grades IV and V of the WFNS scale), or that need prolonged anesthesia after the treatment of the aneurysm itself. As a consequence, in comatose subarachnoid hemorrhage patients, the use of more invasive approaches is warranted. These approaches include monitoring of brain energy metabolism using intraparenchymal probes or catheterization of the jugular vein. Invasive monitoring has been proposed as a way to detect neurochemical alterations predictive of delayed cerebral ischemia and/or of poor long-term outcome. Moreover, invasive monitoring strategies can be used to inform decisions on specific therapeutic actions in patients exhibiting predictive neurochemical alteration profiles.

To assess brain energy metabolism status in subarachnoid hemorrhage patients, two neurochemical approaches are currently available. The first is a "local" approach (Figure 1A), which is based on the implantation of intracerebral probes into cerebral areas at risk. This type of monitoring enables measurements of the concentrations of energy metabolites (e.g., glucose, lactate, pyruvate) by sampling cerebral extracellular fluid using microdialysis. The local approach also allows measurement of in situ brain tissue oxygen tension ($PbtO_2$). The second is a "global" approach (Figure 1B). This method permits evaluation of brain energy metabolism by measuring arterial-venous differences in brain energy biomarkers (e.g., glucose, lactate, and oxygen content).

To perform global monitoring, a catheter is placed in the internal jugular vein for sampling venous blood containing metabolites leaving the brain. A second catheter is located in a peripheral artery for sampling arterial blood metabolites entering the brain. After venous and arterial blood sampling (every 8 h in our protocol), metabolite concentrations are measured using a blood gas analyzer and arterial-venous differences in lactate, glucose, pyruvate, and oxygen content are calculated. Other relevant indices derived from these parameters are also computed. For example, the metabolic ratio is the arterial-venous difference in oxygen content vs the arterial-venous difference in glucose. The lactate-oxygen index can also be calculated, which is the ratio of the arterial-venous difference in lactate concentrations vs the difference in oxygen content. In summary, the "global" approach enables evaluation of the energetic status of the entire cerebral hemisphere.

Several studies have used local or global neurochemical approaches to predict long-term functional outcomes and/or to detect delayed cerebral ischemia. However, most of these studies were retrospective and compared overall neurochemical data between two groups of subarachnoid hemorrhage patients: those with vs those without delayed cerebral ischemia in the context of long-term poor vs favorable outcomes. To quantify long-term outcomes, the Glasgow Outcome Scale was most often used. This scale classifies patients into one of five categories: deceased (GOS 1), vegetative state (GOS 2), severe disability (GOS 3), moderate disability (GOS 4), and positive recovery (GOS 5).

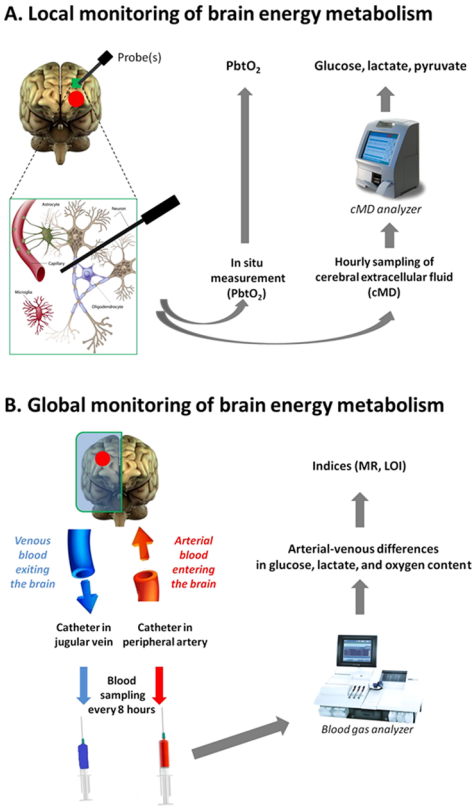

Figure 1. Scheme of (A) local and (B) global neurochemical monitoring approaches for assessing brain energy metabolism in subarachnoid hemorrhage patients. In (A), local monitoring is performed with probes implanted in the brain parenchyma. A brain tissue oxygen tension sensor is used to measure in situ oxygen partial pressures ($PbtO_2$) continuously. Local monitoring is also carried out by implanting a microdialysis probe to perform cerebral microdialysis (cMD) via hourly samples collected from the brain extracellular fluid for immediate bedside determination of concentrations of brain energy metabolism biomarkers (i.e., glucose, lactate, pyruvate) using a commercially available clinical microdialysis analyzer (M Dialysis AB Iscusflex). This local approach provides a time-course recording of changes in brain energy metabolism in a small brain area (green square) where a probe is implanted (at-risk territory near the hemorrhage site represented by the red circle). In (B), the global approach requires implantation of two catheters. One is placed in the internal jugular vein to collect samples for analysis of venous blood energy biomarkers exiting the brain. A second catheter is implanted in a peripheral artery to sample arterial blood for energy biomarker concentrations entering the brain. Every 8 h, glucose, lactate, pyruvate, and oxygen content are measured using a blood gas analyzer together with other typical blood parameters. Arterial-venous differences for a number of neurochemical markers are calculated, including the lactate-oxygen index (LOI) and the metabolic ratio (MR). This global approach gives information on brain energy metabolism in the brain hemisphere (green rectangle) corresponding to the side of the brain where the jugular catheter is placed and the original subarachnoid hemorrhage occurred.

Patients with an "unfavorable" outcome exhibit GOS values of 1, 2, or 3, while subarachnoid hemorrhage patients with a "favorable" outcome have GOS values of 4 or 5.

From those studies based on local monitoring (i.e., clinical microdialysis and $PbtO_2$ levels), neurochemical profiles were correlated with the occurrence of delayed cerebral ischemia and functional outcome. For example, ischemic neurochemical patterns characterized by elevation of lactate/pyruvate ratios (>40), low cerebral glucose levels (<1 mmol/L), increased

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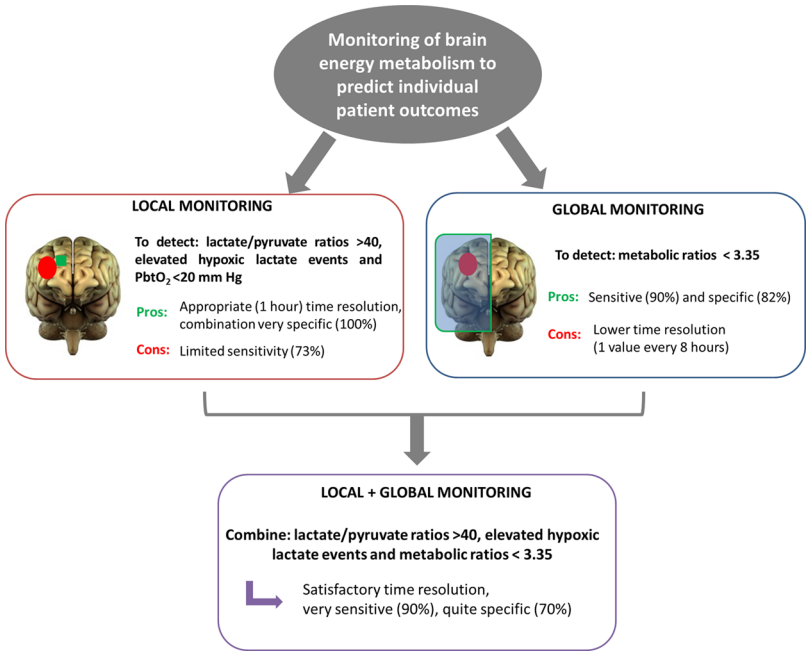

Figure 2. Local vs global monitoring of brain energy metabolism to predict individual outcomes for subarachnoid hemorrhage patients. The red circle represents the hemorrhage site. For local monitoring, the green square represents the brain area monitored by the probes. For global monitoring, the green rectangle represents the whole hemisphere that is monitored by arterial-venous catheters.

cerebral lactate concentrations (>4 mmol/L), and decreased $PbtO_2$ (<20 mmHg) were associated with delayed cerebral ischemia and an unfavorable outcome.[1,2] Importantly, because these neurochemical alterations are detected before the occurrence of delayed cerebral ischemia, they can be used to inform rapid changes in patient treatment to avoid irreversible cerebral damage, such as a cerebral infarct.

The pathophysiological basis of outcome prediction using neurochemical biomarkers should take into account the findings of Oddo et al.[3] that describe two sources of elevated lactate. Each lactate source is differently correlated with long-term outcome. These authors defined metabolic events associated with "hypoxic lactate" corresponding with lactate values >4 mmol/L in association with $PbtO_2$ < 20 mmHg. Here, hypoxic lactate measures were correlated with poor outcome. Alternately, "hyperglycolytic lactate" was defined by lactate values >4 mmol/L in association with pyruvate values >119 μmol/L. Here, high lactate values were correlated with a positive outcome. In an earlier study by Oertel et al. also focused on outcome prediction, the global (arterial-venous) approach was used to show that decreased metabolic ratio values and elevated lactate-oxygen indices were clearly correlated with poor functional outcomes in subarachnoid hemorrhage patients.[4]

However, until now, all correlations between typical neurochemical profiles and functional outcomes were determined only at the aggregate level and none of these studies has considered whether evaluating these profiles at the individual level might improve prediction of long-term outcomes of specific subarachnoid hemorrhage patients during intensive care management. Because of the lack of predictive correlation of individual clinical relevance, neurochemical monitoring of brain energy metabolism has not yet been included in official guidelines for the management of subarachnoid hemorrhage patients. In fact, without clear-cut categorical values, it is difficult to use biochemical data at the individual level to inform therapeutic choices.

It was in this context that we recently revisited the investigation of the use of neurochemical monitoring techniques for individualized patient outcome assessment. Our goals were to determine categorical values for several neurochemical parameters and to identify typical neurochemical patterns that could be used in the NICU for individual management of subarachnoid hemorrhage patients. Specifically, we considered the numbers of metabolic events that were likely to correlate with prognosis. We also performed a receiver-operating characteristic (ROC) curve analysis to identify threshold values that could predict differentially an unfavorable outcome from a favorable one, at the individual level, with a satisfactory performance (area under the curve (AUC) > 0.8). The ROC curve is a fundamental tool for diagnostic test evaluation. In an ROC curve, the true positive rate (sensitivity) is plotted as a function of the false positive rate (100-specificity) for different cutoff points for each parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The AUC is a measure of how well a particular parameter can distinguish between two diagnostic groups (diseased/normal or unfavorable/favorable outcomes in our case). From this ROC curve analysis, it is also possible to choose one decision threshold with sufficient sensitivity and specificity that could be applied in practice for the outcome prediction of all the subarachnoid hemorrhage patients.

We first applied the ROC curve analysis approach to neurochemical values obtained with the local sampling approach. Herein, we retrospectively analyzed biochemical data from 47 patients who were studied simultaneously by intracerebral microdialysis and $PbtO_2$ measurements (article in preparation). Of these 47 patients, 33 presented an unfavorable outcome six months after subarachnoid hemorrhage. We first compared the frequency of the following neurochemical events between the two groups: lactate/pyruvate ratios > 40 (metabolic crisis), low glucose events (glucose <1 mmol/L), episodes of $PbtO_2$ < 20 mmHg (hypoxia), hypoxic lactate events, and hyperglycolytic

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lactate events. Only the frequencies of lactate/pyruvate ratios > 40, hyperglycolytic lactate events, and hypoxic lactate events were significantly different between the two groups.

Our findings support those of the studies reported above by Sarrafzadeh et al. and by Oddo et al. In these studies, lactate/pyruvate ratios > 40 were more frequent in patients with an unfavorable outcome than in patients with a favorable outcome, while hyperglycolytic lactate events were more frequent in the group of patients with a favorable outcome. Interestingly, hypoxic lactate events were observed only in patients with an unfavorable outcome. With the ROC curve analysis, we found that only one type of neurochemical profile, the one with the occurrence of hypoxic lactate events, showed acceptable performance to predict the outcomes at the individual level (AUC = 0.83). Indeed, the occurrence of at least one hypoxic lactate event predicted an unfavorable outcome with a sensitivity of 65% and a specificity of 100% (Figure 2). Furthermore, we showed that in this series of 47 patients, the combination of three metabolic profiles, (>1 hypoxic lactate event, >1 event of a lactate/pyruvate ratio > 40, and >13 events of $PbtO_2$ < 20 mmHg) improved the sensitivity to 73% while maintaining 100% of specificity (Figure 2).

In a second study, we applied the same procedure to the blood parameters obtained using the global approach.[5] We conducted data analysis of 68 patients, including 40 patients presenting unfavorable outcomes (GOS 1−3). In this study, we compared the results of the blood parameters between the two prognostic groups. As anticipated, we observed that patients with unfavorable outcomes were characterized by higher arterial-venous lactate levels, higher lactate-oxygen indices, and lower metabolic ratios vs patients with favorable outcomes. When we considered the frequencies of these metabolic events, the same differences were observed. Applying an ROC curve analysis of the numbers of events, we were able to identify a unique neurochemical criterion, metabolic ratio values < 3.35 that exhibited an excellent predictive value. As such, metabolic ratio may be of high interest for the individualized management of patients with subarachnoid hemorrhage (Figure 2). Indeed, in this series of 68 patients, the occurrence of at least three metabolic ratio values < 3.35 was predictive of a poor outcome with a sensitivity of 90% and a specificity of 82% (AUC = 0.88).[5]

In the present case (i.e., neurochemical prediction of delayed cerebral ischemia and poor outcome), the results appear to justify priority for sensitivity because confirmation tools exist (i.e., cerebral imagery). However, while assessment of global metabolic ratios seems to provide improved accuracy for predicting individualized outcome with a greater sensitivity than intracerebral microdialysis parameters and $PbtO_2$ monitoring, its time-resolution remains low (sampling only every 8 h) as compared with the temporal resolution of local microdialysis and $PbtO_2$ monitoring where sampling occurs at least once per hour. Taking these respective characteristics into consideration, we decided to test the association of local *and* global monitoring in the same patients to predict long-term functional outcomes. For such a study, we retrospectively analyzed neurochemical data from 18 subarachnoid hemorrhage patients including 11 patients who eventually had poor functional outcomes 12 months after their initial hemorrhage event.[6] As in the two previous studies, we observed that the numbers of lactate/pyruvate ratio events > 40 was a sensitive yet nonspecific criterion to predict an unfavorable outcome, while hypoxic lactate events were a specific marker of an unfavorable outcome. Moreover, the number of low metabolic ratio events was the neurochemical marker with the best performance for predicting an unfavorable outcome. Interestingly, we showed that consideration of at least two of these three profiles improved prediction over each profile alone. Indeed, this approach enabled prediction of an unfavorable outcome with a sensitivity of 90% and a specificity of 70% (Figure 2). It is worth mentioning that local and global monitoring techniques are complementary and their association leads to good predictive validity of patient outcome with temporal-resolution better that obtained using global monitoring by itself.

When taken together, the studies discussed above show that clinical neurochemistry monitoring of brain energy metabolism, locally, globally, or better yet via the combination of the two, should be integrated into standard NICU practice, particularly for comatose patients, because of the likely added value in individualized outcome prediction and management of subarachnoid hemorrhage patients. Moreover, we advocate for much needed prospective clinical validation of this approach for subarachnoid hemorrhage patients but also for patients with other types of traumatic brain injury. Such a clinical neurochemistry-based strategy is likely to assist in the detection of critical risk periods. Moreover, identifying such periods will enable the design and conduct of prospective clinical studies aimed at evaluating the potential benefits of timely ("real-time") interventional strategies and/or therapies based on individual human brain neurochemical information.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: yannick-tholance@hotmail.fr.

*E-mail: bernard.renaud@univ-lyon1.fr.

Notes

The authors declare no competing financial interest.

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