



Cerebral Energy Status and Altered Metabolism in Early Brain Injury After Aneurysmal Subarachnoid Hemorrhage: A Prospective 31P-MRS Pilot Study

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Background: Acute changes of cerebral energy metabolism in early brain injury (EBI) after aneurysmal subarachnoid hemorrhage (aSAH) may play a crucial role for overall neurological outcome. However, direct detection of these alterations is limited. Phosphorous magnetic resonance spectroscopy (31P-MRS) is a molecular-based advanced neuroimaging technique allowing measurements of pathophysiological processes and tissue metabolism based on various phosphorous compound metabolites. This method may provide objective assessment of both primary and secondary changes.

Objective: The aim of this pilot study was to evaluate the feasibility and the diagnostic potential of early 31P-MRS in aSAH.

Methods: Patients with aSAH treated for ruptured aneurysms between July 2016 and October 2017 were prospectively included in the study. 3-Tesla-MRI including 31P-MRS was performed within the first 72 h after hemorrhage. Data of the vascular territories of the anterior, middle, and posterior cerebral arteries (ACA, MCA, PCA) and the basal ganglia were separately analyzed and compared with data of a healthy age- and sex-matched control group. Phosphorous compound metabolites were quantified, and ratios of these metabolites were further evaluated. Influence of treatment modality, clinical conditions, and analgosedation were analyzed.

Results: Data of 13 patients were analyzed. 31P-MRS showed significant changes in cerebral energy metabolism after aSAH in all cerebrovascular territories. Both PCr/ATP and PCr/Pi ratio were notably increased ($P < 0.001$). Also, Pi/ATP was significantly decreased in all cerebrovascular territories ($P = 0.014$). PME/PDE ratio was overall significant decreased ($P < 0.001$).

Conclusion: 31P-MRS is a promising non-invasive imaging tool for the assessment of changes in energy metabolism after aSAH. It allows a detailed insight into EBI and seems to harbor a high potential for clinical practice.

Keywords: brain metabolism, early brain injury, subarachnoid hemorrhage, 31-P-MR-spectroscopy, energy status

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) and the associated early brain injury (EBI) are accompanied by a complex series of secondary pathophysiological cascades, leading to global alterations of the cellular environment and energy metabolism (1–3).

Detecting these changes in cerebral energy metabolism and mitochondrial dysfunction might be crucial for further treatment and assessment of overall neurological outcome, yet to date it is inconceivable only with the use of conventional neuroimaging methods. Multimodal cerebral neuromonitoring (i.e., brain tissue oxygenation and cerebral microdialysis) represents one of the sporadic options to identify clinically relevant pathophysiological alterations and their development. However, these methods estimate changes only locally, with no possibility to evaluate the complex situation in the entire brain (4–6). Moreover, multimodal cerebral monitoring is an invasive neurosurgical procedure associated with potentially relevant surgery-related complications (7).

In contrast, magnetic resonance spectroscopy (MRS) allows non-invasive measurements of selected metabolites, in case of 31P-MRS phosphorous compound metabolites (8), potentially providing comprehensive insights into posthemorrhagic pathophysiological processes with objective assessment of tissue damage, altered cerebral metabolism, and “tissue at risk” in a non-invasive manner. Furthermore, the early phase after aSAH and the underlying cerebral energy metabolic changes have not yet been sufficiently clarified.

To the best of our knowledge, there are only few clinical series employing 31P-MRS in aSAH, all with small numbers of patients and variable time points when 31P-MRS was performed. Interestingly, in animal models of aneurysm rupture, numerous changes in energy metabolism have been reported, however with inconsistent findings (9–12) and limited transferability to humans.

The aim of our study was to evaluate energy metabolism in EBI (<72 h) after aSAH using 31P-MRS to detect relevant energy alterations, additionally compared to age- and sex-matched healthy controls.

We therefore prospectively analyzed 13 consecutive aSAH patients with ruptured intracranial aneurysms who underwent an early MRI including 31P-MRS performed within the first 72 h after SAH in order to thoroughly evaluate all cerebral areas and cerebrovascular territories, to detect changes of cerebral energy metabolism, gaining a better understanding of complex pathophysiological processes during EBI after aSAH.

MATERIALS AND METHODS

Patients older than 18 years of age with aSAH who were admitted to our Department between July 2016 and October 2017, were prospectively included in the study. Depending on clinical parameters and aneurysm morphology, patients underwent microsurgical clipping or endovascular coil embolization after interdisciplinary decision and the intervention was carried out within 24 h. An early MRI was performed within 72 h after the hemorrhagic event. Exclusion criteria were contraindications to MRI (e.g., pacemaker, metal objects), or an unstable clinical condition disqualifying the patient to undergo an MRI examination safely. As the effect of mechanical ventilation and analgosedation on cerebral metabolism assessed by MRS has not yet been thoroughly clarified, patients were dichotomized according to sedation and ventilation for analysis.

The effect of treatment modality remains unclear, as a craniotomy is considered more invasive and may possibly have an additional influence on cerebral metabolism. Besides, given the anatomical and location differences between the surgically and endovascularly treated aneurysms, we additionally performed a statistical subanalysis with patients dichotomized by the treatment modality.

A total of 13 patients met the inclusion criteria and were prospectively enrolled in the study. Detailed demographic data are summarized in **Table 1**. Upon admission, aSAH patients were evaluated with computed tomography (CT) and CT angiography (CTA), complemented with cerebral catheter angiography in most cases. Also, invasive cranial multimodal neuromonitoring was inserted if indicated and further ultra-early aneurysm treatment routinely undertaken within the first hours after admission. As mentioned above, all MRI scans were performed within 72 h after SAH. Of note, the mean arterial blood pressure was continuously kept at a level of >80 mmHg, as it is standard in the management of aSAH patients at our site to ensure adequate cerebral perfusion. To achieve this, norepinephrine was administered continuously through a central venous catheter and the dose was adjusted accordingly. Midazolam and sufentanil were administered for standardized general analgosedation.

To allow comparison of cerebral energy metabolism with a healthy population, 13 healthy control subjects were matched (age/gender) and analyzed. All MRI examinations were performed using the same 3 Tesla device (see below). The study was approved by the Local Ethics Committee of the Medical University Innsbruck (Protocol number: AN2016-0032 359/4.8). Written informed consent was obtained according to Austrian law either from the patient when regaining consciousness and legal capacity, or from her/his guardian.

Magnetic Resonance Imaging

All patients underwent standard MRI performed on a 3T whole-body system (Verio, Siemens Medical AG, Erlangen, Germany). 31P-MRS was performed on the same MRI unit with a double-tuned 1H/31P volume head coil (Rapid Biomedical, Würzburg, Germany). For each patient, one MRS 3D block based on a previously acquired T2 space sequence of the entire brain was recorded, resulting in an extrapolated $16 \times 16 \times 8$ matrix and a field of view of $240 \times 240 \text{ mm}^2$, with a single voxel size of $15 \times 15 \times 25 \text{ mm}^3$. For 31P-MRS data evaluation, voxels of interest were selected from all cerebrovascular territories (ACA, MCA, PCA, and basal ganglia separately). See **Figure 1**.

In the healthy control group, data designated for comparison were collected from the same cerebrovascular territories and selected areas of matched patients anatomically corresponding with the voxels of interest. 31P-MRS data were processed offline with the jMRUI software package (version 5.0, available at: <http://www.mrui.uab.es>), utilizing the non-linear least square fitting algorithm AMARES (13). Phospho-creatine (PCr), adenosine-tri-phosphate (ATP), free phosphate (Pi), phosphomonoester (PME), and phosphodiester (PDE) were determined from each voxel of interest. Although still a matter of debate, defined metabolite ratios have been introduced as surrogate parameters for crucial processes in cellular metabolism (14). Accordingly, ratios representing ATP resynthesis (PCr/ATP), ATP hydrolysis (Pi/ATP), energy demand (PCr/Pi), and membrane turnover (PME/PDE) were used and calculated for the structurally affected tissue as well as the aforementioned cerebrovascular territories and these ratios were compared with the corresponding brain regions of the healthy control group (15–17).

Importantly, absolute values of phosphorus metabolites may not be simply used for reliable interpatient comparison given the significant differences between the individuals. Thus, various ratios of phosphorous metabolites are routinely used here. Accordingly, we interpreted PCr/ATP-ratio as an indirect measure of ATP resynthesis as previously described by Wallimann et al. (17), Pi/ATP ratio as ATP hydrolysis, PCr/Pi ratio as a tissue energy demand and PME/PDE ratio as a membrane turnover as described by Liu et al. (14).

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics (V.21, version 21, SPSS Inc., IBM, Chicago, IL, USA). Continuous variables were reported as mean values and confidence intervals. The calculated ratios were tested for normality using the Shapiro-Wilk test. Also, ANOVA was performed to check for significant differences. Differences with a *P*-value of <0.05 were considered statistically significant.

RESULTS

A total of 13 patients (aged 34–70 years, mean 54.5 years; 11 female and 2 male patients) with aSAH were enrolled in the study. The most common initial clinical presentation according to the Hunt&Hess classification and WFNS classification was grade 1 in seven patients (53.8%), followed by grade 2 in two patients (15.4%), and grade 3 in three patients (23.1%). One

TABLE 1 | Demographic data of all included patients.

13 patients	Male	2	
	Female	11	
Age (years)	54.5	Range	34–70
H&H class	1	7	
	2	2	
	3	3	
	4	1	
	5	0	
Treatment	Surgical	9	
	Endovascular	4	
Localization	ACOM	5	
	ACI	1	
	MCA	2	
	PCOM	3	
	DACA (pericallosal artery)	2	
EVD/monitoring	None	6	
	EVD/monitoring	7	

ACOM, anterior communicating artery; ACI, internal carotid artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; DACA, distal anterior cerebral artery or pericallosal artery; EVD, external ventricular drain.

patient presented with Hunt&Hess grade 4 (7.7%). Detailed demographic data are summarized in **Table 1**.

After aneurysmal SAH, there was a globally increased PCr/ATP ratio in all ROIs representing the state of ATP resynthesis ($P < 0.001$). Pi/ATP ratio reflecting the ATP hydrolysis conditions was notably decreased ($P = 0.014$), resulting in global impairment of ATP utilization in all cerebrovascular territories. PCr/Pi ratio representing tissue energy demand was significantly increased after aSAH in all cerebrovascular territories ($P < 0.001$). PME/PDE ratio standing for membrane turnover significantly different between the healthy control group and aSAH patients, favoring the healthy controls ($P < 0.001$). Results are summarized in **Table 2** and seen in **Figure 2**.

Given the potential impact of analgesation and mechanical ventilation on 31P-MRS results, we dichotomized our patients into two groups. Three patients (23.1%) were analgesated and mechanically ventilated at time of MRI examination, 10 patients (76.9%) underwent the MRI awake. There were significant alterations in the following ratios between the groups performing ANOVA: PCR/ATP ratio ($p < 0.001$), PCR/Pi ratio ($p < 0.001$), Pi/ATP ratio ($P = 0.049$), and PME/PDE ratio ($P < 0.001$).

When considering the used treatment modality for the ruptured aneurysms, there were apparent changes in all PCR/ATP, PCR/Pi, Pi/ATP, and PME/PDE ratios between the healthy control group and all treated patients (see the **Figure 3**). Yet, energy cerebral metabolism did not differ between the surgically and endovascularly treated patients.

Importantly, all changes in the aforementioned ratios proportionated to both severity of aSAH and initial clinical patient condition. Performing ANOVA, there were impairments in PCr/ATP ratio ($P < 0.001$), PCr/Pi ratio ($P < 0.001$), Pi/ATP

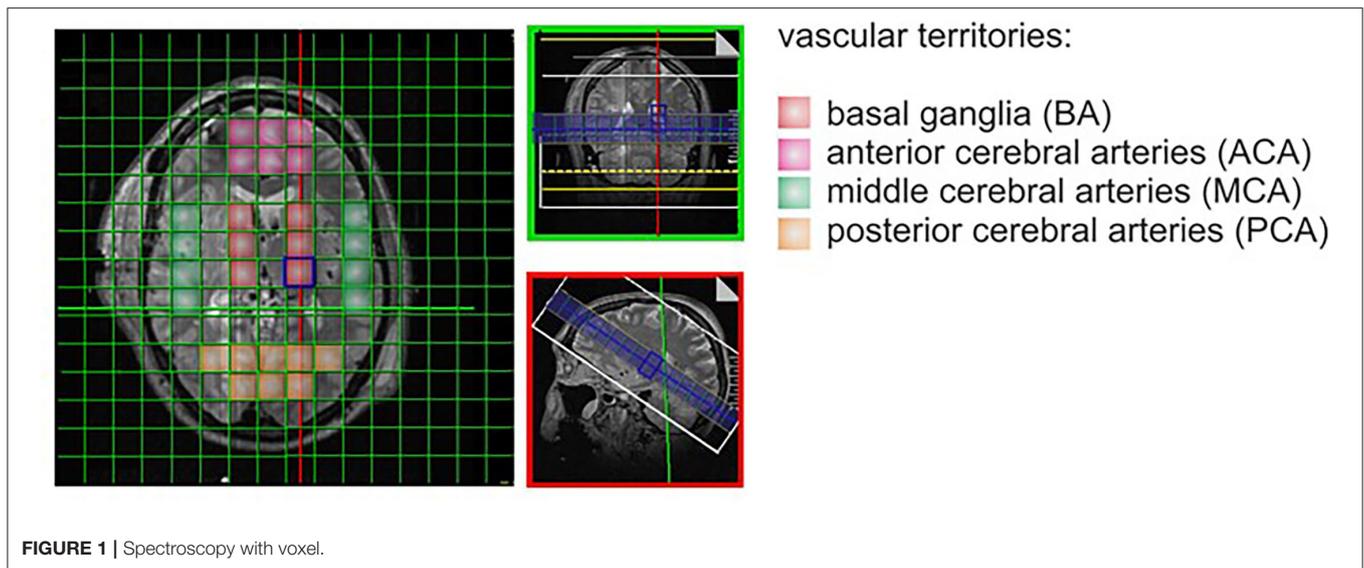


FIGURE 1 | Spectroscopy with voxel.

TABLE 2 | ANOVA, ratios of phosphorous metabolites.

Overall	Patients mean (CI)	Controls mean (CI)	<i>P</i> -value
PCr/ATP	1.1238 (1.1780–1.2698)	1.1098 (1.0824–1.1371)	<i>P</i> < 0.001
PCr/Pi	4.5417 (4.2975–4.7859)	3.7722 (3.6305–3.9140)	<i>P</i> < 0.001
Pi/ATP	0.3273 (0.3096–0.3450)	0.3531 (0.3424–0.3638)	<i>P</i> = 0.014
PME/PDE	0.8099 (0.7557–0.8640)	0.9377 (0.8867–0.9886)	<i>P</i> < 0.001

PCr, Phosphocreatine; Pi, inorganic phosphate; ATP, adenosine triphosphate; PME, phosphomonoester; PDE, phosphodiester.

ratio (*P* = 0.011), and PME/PDE ratio (*P* = 0.017). Results are summarized in **Figure 4** and **Table 3**.

DISCUSSION

This prospective pilot study of 13 patients with aSAH undergoing early MRI within 72 h after hemorrhage provides first comprehensive data on 31P-MRS in EBI after aSAH. These indicate highly significant global alterations in cerebral energy metabolism in all cerebrovascular territories independently of aneurysm location.

Compared to healthy controls there were several significant alterations in cerebral energy metabolism in the acute stage of aSAH. We found a substantial increase of the PCr/ATP ratio representing a lacking resynthesis of ATP in aSAH patients alongside with an altered membrane turnover, expressed as a lower PME/PDE ratio in contrast to the healthy control group. Interestingly, our data indicate an impaired ATP degradation after aSAH, reflected by substantially decreased Pi/ATP ratio differences between the SAH-affected patients and the healthy age- and sex-matched control group. Energy demand was accordingly reduced, represented by an increased PCr/Pi ratio. This implies major disturbances of the cerebral energy metabolism, not only in terms of ATP synthesis but also at

the level of ATP utilization in the entire brain. These findings of decreased Pi/ATP ratios in EBI due to aSAH appear to be similar to them after traumatic brain injury (TBI) as shown in human subjects by Garnett et al. (18). Likewise, Pinggera et al. found recently similar changes in brain metabolism in the acute state in after severe TBI (19, 20). Stovell et al. analyzed PCr/ATP ratios in a small group of patients in the acute state after traumatic TBI using 31P-MRS and correlated these findings with tissue NADH/NAD⁺ after succinate supplementation (21). They found no global significant changes in PCr/ATP ratios yet a subgroup of patients with mitochondrial dysfunction presented with increased PCr/ATP ratio. In contrast, in our current study, PCr/ATP ratio was substantially increased in all cerebrovascular territories, strongly indicating a complex cerebral energy metabolism impairment including disturbed ATP resynthesis in acute brain injury after aneurysmal SAH. Likewise, numerous cerebral metabolic functions seem to be impaired after TBI also in animals as shown by Yoshino et al. In their rat model simulating cerebral concussion with no evidence of direct morphological damage the authors studied several metabolic processes within the first 10 days after TBI. They reported an early rather global metabolic depression which lasted for as long as 5 days. Their results indicated dramatic alterations in cell metabolic functioning (22).

31P-MRS obviously allows insight into cerebral energy metabolism in a non-invasive way. In defiance of the challenging character of MRI in critically ill patients and possible technical difficulties associated with required MR-compatibility, we have demonstrated that early MRS after aSAH is technically feasible, representing a promising non-invasive tool for comprehensive unbiased assessment of brain damage and posthemorrhagic “tissue at risk.”

In our study, mean arterial blood pressure was continuously kept above 80 mmHg in order to eschew hypotension-induced hyperperfusion and its resultant potential distortion of the findings. There were no relevant MRI-related adverse events

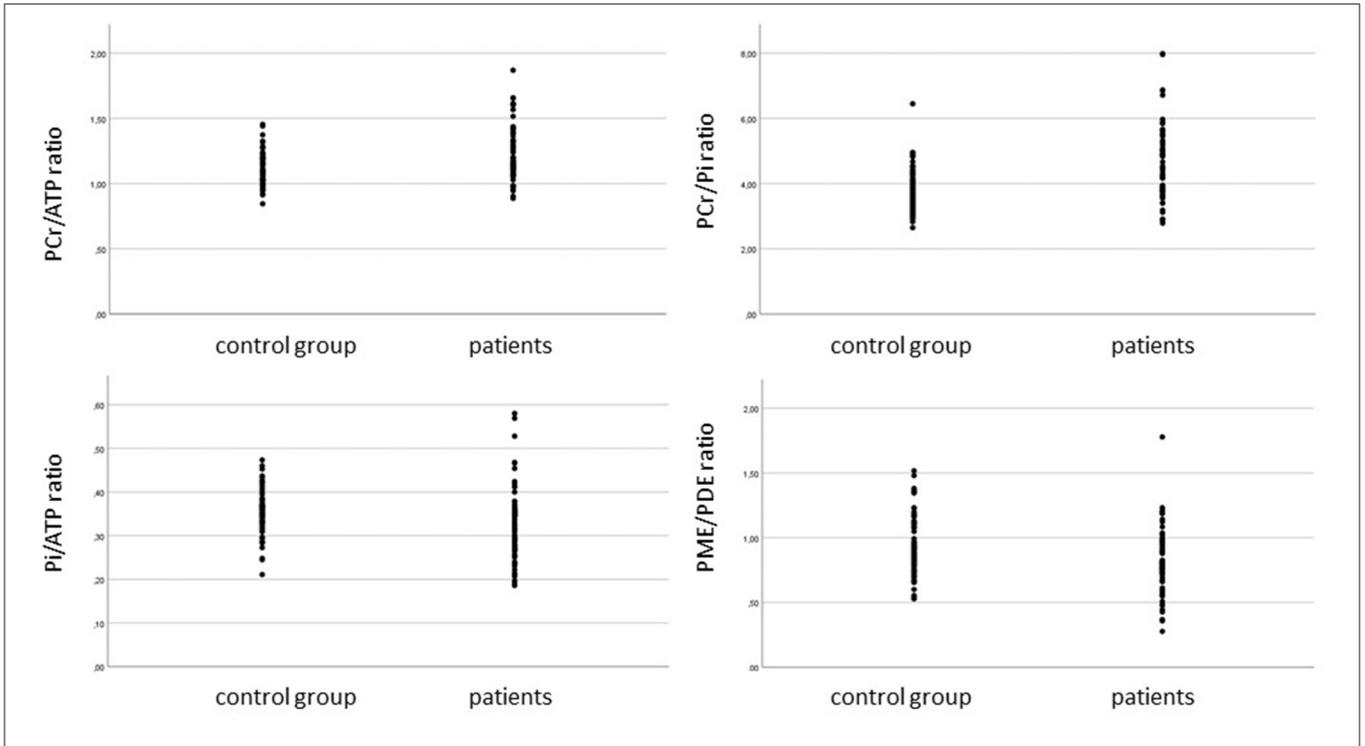


FIGURE 2 | PCr/ATP ratio, PCr/Pi ratio, Pi/ATP ratio, and PME/PDE ratio in SAH patients and control group. ANOVA performed.

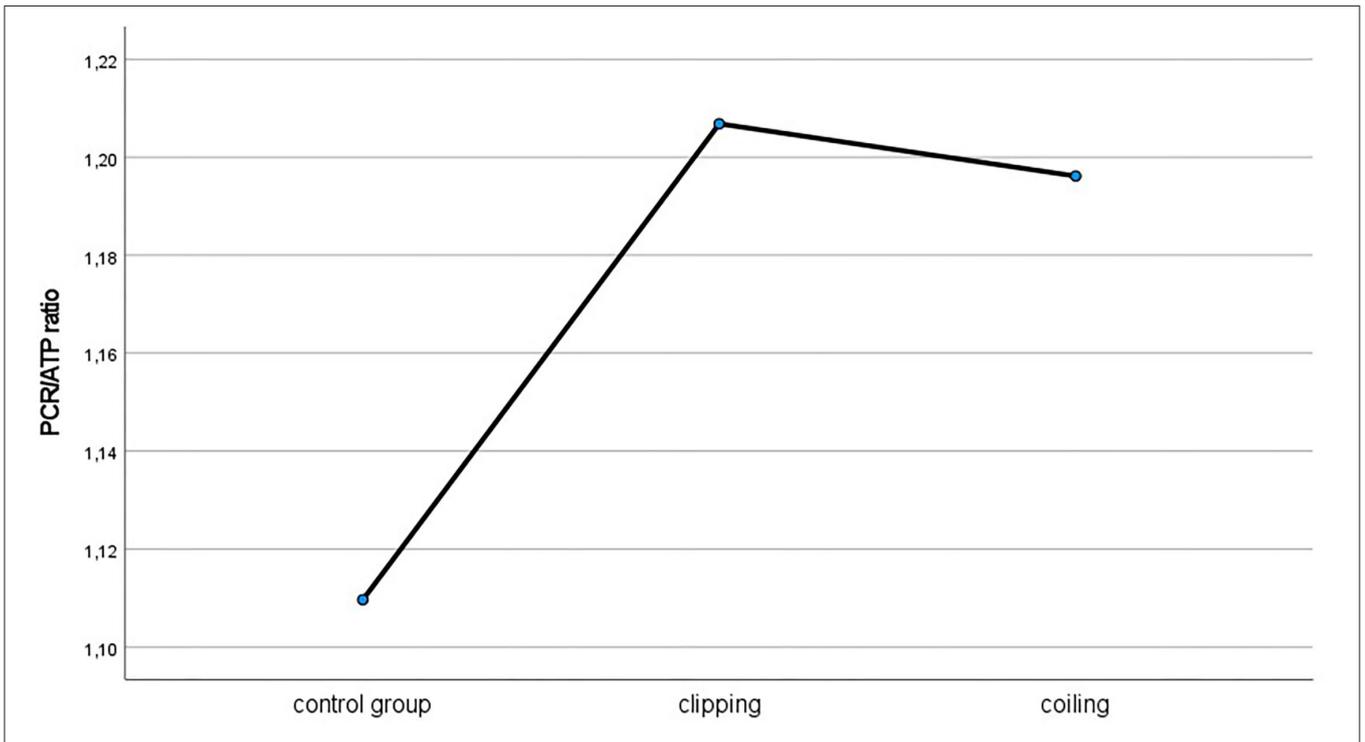
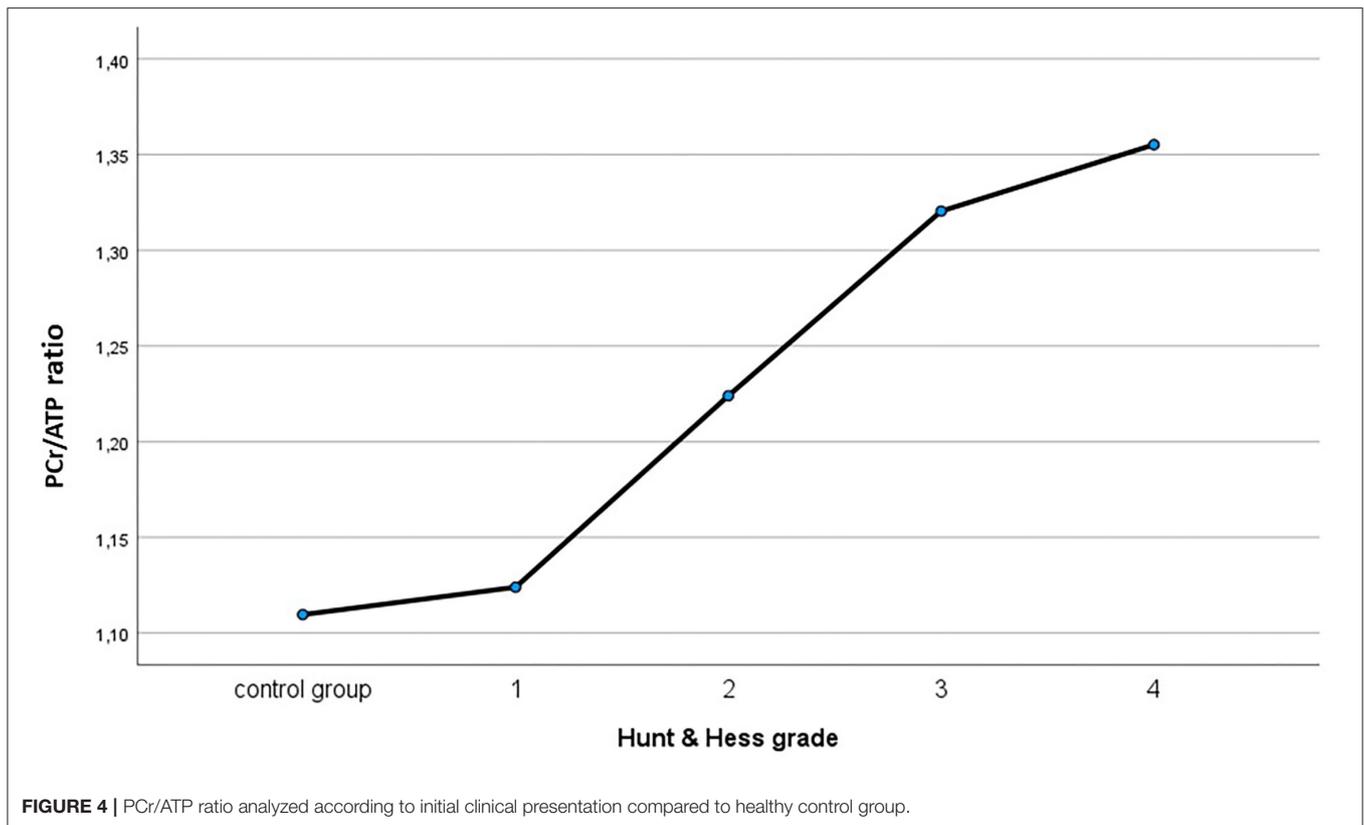


FIGURE 3 | PCr/ATP ratio in patients treated microsurgically and endovascularly compared to healthy control group.



or clinical deterioration. Likewise, the safety and feasibility of advanced MRI examinations in critically ill patients have been recently affirmed in 26 patients with severe TBI, who underwent an early MRI without any additional risk or morbidity (23).

A decrease of PCr/ATP levels has been described in a rat model with induced SAH-like events (11). In a monkey model Handa et al. showed a reduction of ATP during induced hypotension and therefore suspected a correlation between changes in brain metabolism and a reduced CBF due to impaired autoregulation (12). Schubert et al. found a significant reduction of CBF within the first 12 h after aSAH examined with Xenon-CT in humans, which was independent from CPP and ICP (24). This hypoperfusion correlated with the initial clinical presentation, i.e., SAH grade, but was present globally even in low-grade SAH. Interestingly, our 31P-MRS measurements also demonstrated a global affection of the brain, even though the majority of patients presented with lower SAH grades being in good clinical condition. Early brain injury appears thus characterized by global cerebral metabolic changes. We found the cerebral metabolism altered not only in voxels adjacent to the ruptured aneurysm but also in all other cerebrovascular territories.

Our results indicate an increased ratio of PCr/Pi, so that aSAH most likely escalates global energy demand in the acute phase of the disease. Steiger et al. showed a decreased Pi/PCr ratio in less perfused areas in a patient with giant cell arteritis and high-grade stenosis of the vertebral artery and the internal carotid artery (25). Based on our apparent findings we esteem 31P-MRS for a

promising non-invasive tool how to assess pertinent metabolic changes in all cerebrovascular territories at a subcellular level, and not only locally depending on neuromonitoring probe positioning. Importantly, the interpretation of our findings must be performed carefully due to the small number of the included patients. Yet, we assume that the differences may become even more apparent in case of larger study group.

31P-MRS is being routinely used to examine metabolic changes in other intracranial lesions such as tumors or psychiatric diseases (26–28). Also, some animal studies investigated TBI and subsequent effects on brain metabolism as well as on magnesium levels (29, 30). Ishige et al. showed an overall decrease of ATP and PCr after TBI in a rat model (31). Similarly, several clinical series examined trauma-related changes in energy metabolism and magnesium levels in humans (32–34). For example, Garnett et al. performed 31P-MRS in TBI patients after a mean of 9 days (range 2–21 days) and found a significant decrease of pH and magnesium in cerebral tissue as well as elevated ratios of PCr/Pi and PCr/ATP, while the Pi/ATP ratio was decreased (18).

It is worthy of notice that MRI in ventilated patients in an early stage is highly challenging and related to numerous critical care issues (23). Furthermore, to date it has not been sufficiently elucidated yet whether and how mechanical ventilation and analgesation commonly applied in both preclinical and clinical studies affect brain oxygenation and cerebral energy metabolism and the related 31-P-MRS findings under the analgesation. In

TABLE 3 | ANOVA, analysis regarding initial clinical presentation, treatment modality, analgosedation, and ventilation and inserted EVD and monitoring.

	PCR/ATP ratio	PCR/Pi ratio	Pi/ATP ratio	PME/PDE ratio
Cerebrovascular territories	$P < 0.001$	$P < 0.001$	$P = 0.011$	$P = 0.017$
Treatment modality	n.s.	n.s.	n.s.	n.s.
Analgosedation and mechanical ventilation	$P < 0.001$	$P < 0.001$	$P = 0.049$	$P < 0.001$
EVD and monitoring	n.s.	n.s.	n.s.	n.s.
Initial clinical presentation	$P < 0.001$	$P < 0.001$	$P = 0.031$	$P < 0.001$

PCr, Phosphocreatine; Pi, inorganic phosphate; ATP, adenosine triphosphate; PME, phosphomonoester; PDE, phosphodiester; EVD, external ventricular drain.

our study we found substantial global changes in the cerebral energy metabolism in both intubated and conscious patients indicating that the 31P-MRS is feasible and reliable also under the terms of anesthesia.

We acknowledge that our study has several limitations. Certainly, the results must be interpreted carefully in the light of the small sample size evaluated. A comparison of alterations between the hemispheres or an investigation of the possible impact of aneurysm location were thus only finite. Additionally, the voxel size is rather large, making a differentiation between gray and white matter arduous. Also, it is worth noticing that the majority of the included patients in our pilot study presented with low-grade hemorrhage. This represents a certain bias in patient selection for high-grade SAH patients present with rather unstable clinical conditions and the advanced MRI examinations remain challenging in the neurointensive care patients (19).

It may have resulted in possible distortion of our findings toward difference mitigation between the SAH patients and the healthy control group. Given the current apparent differences in our study, if including also the high-grade hemorrhages one may expect even stronger divergence between the groups.

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The limitations notwithstanding, our findings and the results from the aforementioned previous studies produced consistent results and comparable data.

CONCLUSION

The highly significant changes in cerebral energy metabolism in all cerebrovascular territories mirrors the complexity of EBI after aneurysmal SAH, indicating a global impairment of cerebral metabolism at multiple levels. This prospective clinical trial using 31P-MRS identifies MRS as a possible promising advanced neuroimaging technique in the acute stage of SAH. It may provide a better understanding and a more detailed insight into the pathophysiological metabolic processes and interactions after aneurysmal SAH in a non-invasive fashion. Yet, future studies are needed with larger number of patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee of the Medical University Innsbruck (Protocol Number: AN2016-0032 359/4.8). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ST, AG, CT, and OP: conception or design of the work. ST, WH, RS, AR, and OP: data collection. ST, WH, RS, AG, AR, EG, CT, and OP: data analysis and interpretation. ST and OP: drafting the article. All authors critical revision of the article and final approval of the version to be published.

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