ARTYKUŁ ORYGINALNY/ORIGINAL PAPER

Impact of arterial blood homeostasis on cerebral metabolism and incidence of secondary ischemia – Reliability of neurochemical monitoring in patients with severe subarachnoid hemorrhage. A preliminary report

Jens Soukup[1,4], Patrick Kellner[1], Matthias Joachim Langer[3], Matthias Menzel[2]

[1] Department of Anaesthesia and Critical Care, Martin-Luther-University Halle-Wittenberg, Germany
[2] Department of Anaesthesia and Critical Care, Community Hospital Wolfsburg, Germany
[3] Department of Anaesthesia and Critical Care, Community Hospital Köthen GmbH, Germany
[4] Department of Anaesthesia, Critical Care and Palliative Care, Carl-Thiem Hospital, Cottbus, Germany

Abstract

Background. The present analysis of patients with aneurismal subarachnoid hemorrhage addresses the question of how far systemically administered energy substrates or medication during intensive care management can significantly influence cerebral metabolism and must therefore be considered when interpreting the results of cerebral microdialysis. *Methods.* An intracerebral microdialysis catheter was implanted in 13 patients with aneurysmal subarachnoid hemorrhage after aneurysmatic clipping. The extracellular concentrations of glucose, lactate, glutamate and glycerol were determined by bed-side analysis together with systemic parameters (blood glucose, insulin and noradrenalin administration). To test our setup in patients with severe aneurysmal subarachnoid hemorrhage typical symptoms, the incidence of secondary cerebral ischemia and cerebral vasospasm, were analyzed in relationship to the course of the measured parameters by cerebral microdialysis. *Results.* The glucose levels in the microdialysate showed a tendency to be dependent on the systemic glucose concentration, as long as cerebral ischemia was not present. Furthermore there were 7 cases of temporary hypoglycemia mainly in patients with cerebral ischemia (n = 5). Administration of noradrenalin and insulin had no influence on the measured systemic and local metabolic parameters or insulin therapy. The same applies to the administration of glucose or fat during the nutritional therapy. *Conclusion.* The hypothesis that the glucose level in brain tissue is influenced by the serum glucose levels is valid as long as cerebral ischemia is not present. Systemic administration of energy carriers during parenteral nutrition as well as noradrenalin and insulin does not lead to a relevant effect on the results of cerebral microdialysis. *Anestezjologia i Ratownictwo 2011; 5: 290-299.*

Keywords: subarachnoid hemorrhage, cerebral microdialysis, glucose, cerebral vasospasm, cerebral ischemia

Background

The worldwide annual incidence of cerebral aneurysms amounts to 0.2-9.9% [1]. The outcome in these patients is mostly dependent on the extent of primary neurological damage as well as the resulting secondary brain damage, which often develops with a time delay of several hours up to several days. One of the most common causes of secondary cerebral ischemia is considered to be the occurrence and severity of cerebral vasospasms and known as delayed ischemic neurological deficit (DIND) when clinical symptoms are present. In contrast acute focal neurological deficits (AFND) are directly related to the cerebral hemorrhage event [2]. Because of the complexity of the disease there are increased requirements on the intensive care monitoring methods, to ensure an adequate and timely detection of the extent of primary damage and simultaneously the early recognition of the development of secondary brain damage. Neuromonitoring represents not only a support for therapy and determination of the prognosis but is also an essential component of the neuroprotective strategy [3-5].

A modern intensive care treatment concept incorporates special therapeutic approaches and strategies in addition to the classical neurosurgical focus of avoiding relevant operative complications (e.g. acute secondary hemorrhage and hydrocephalus) and early recognition and/or prevention of secondary brain damage.

Retrospective analyses of the patients with primary neurological conditions showed that these patients have an increased risk of respiratory problems, especially infections. Therefore they have a poorer outcome than other intensive care patients. Hyperglycemia is also much more common in these patients than other intensive care patients [1]. In recent years the effect of blood glucose levels on the outcome of intensive care patients has increasingly become a subject of scientific discussion [6-9]. Van den Berghe et al. showed that a strict control of blood glucose led to a decrease in infections, but there was a danger of undesired hypoglycemia with negative effects on patient outcome [10,11]. However, the results of the NICE-SUGAR study with 6,104 patients showed that the 90 day mortality of patients with normoglycemia (blood glucose 81-108 mg/dl) was significantly higher than those with blood glucose levels of 144-180 mg/dl (odds ratio 1.14, 95% CI 1.07-1.31, $p = 0.02$) [12].

Studies about the influence of blood glucose management during intensive care therapy especially for patients with severe neurological damage are limited. It is therefore necessary to evaluate the general intensive care therapy concepts further, to adapt this to the special, in this case neurological condition and therefore to further development. In the current literature cerebral microdialysis has proven to be an established method for early recognition of secondary damage, especially in connection with the occurrence of cerebral vasospasms, on the basis of alterations in concentrations of neurochemical substances measured in the extracellular space of brain tissue as the correlate of local metabolism [3,5,13-17].

The aim of our clinical study was firstly to determine to what extent clinical questions (determination of insufficient perfusion, secondary cerebral ischemia etc.) can be mirrored in the daily routine by using microdialysis using our own set-up. A further aim was to analyze the effect of systemic interactions on parameters of cerebral metabolism (e.g. glucose, lactate, glutamate and glycerol) during administration of, for example catecholamines and insulin.

Method

The patient study is part of an investigation protocol for the administration of a multimodal neuromonitoring of intensive care patients with severe neuronal damage, which was approved by the local ethics committee.

The study included intensive care patients (age > 18 years) with aneurysmal subarachnoid hemorrhage. As the patients were not able to give their consent, approval for inclusion in the study was obtained after prior confirmation of the official representative.

At the beginning of the extended neuromonitoring the patients received analgosedation and controlled mechanical ventilation. The analgosedation was carried out in the first 3 days of the intensive care treatment with propofol (3-6 mg/kg body weight/h) and remifentanil (0.1-0.25 µg/kg body weight/h). After day 4 analgosedation was switched to midazolam (5-7 mg/h) and sufentanil (30-50 µg/h). All patients received a cerebral perfusion pressure (CPP)-oriented therapy regimen with a target CPP of > 70 mmHg. If this target could not be achieved after adequate volume therapy continuous catecholamine was administered.

Patient monitoring

The standard monitoring includes the continuous recording of arterial blood pressure and heart rate (electrocardiogram ECG), peripheral oxygen saturation (SpO$_2$), central venous pressure (CVP) and recording of the ventilation parameters. Temperature was measured via the urinary bladder.

The extended neuromonitoring included an intraparenchymal intracranial pressure monitoring (ICP Express, Codman, UK) and an interstitial cerebral microdialysis catheter (CMA 70, CMA Microdialysis, Sweden) which was perfused with a sterile 0.9% NaCl at a flow rate of 0.3 µl/min. The extracellular concentrations of glucose, lactate, glutamate and glycerol were measured photometrically at the bedside.

Implantation of the intracerebral monitoring was carried out during the operative treatment of the aneurysm. The microdialysis catheter was placed in the supposed cerebral region, supplied by the injured vessel in all patients. A computed tomography (CT) was carried out to confirm the placement of the implanted probe. Further CT-scans were routinely done on postoperative days 2 and 3 and then every 7 days. The diagnosis of secondary cerebral ischemia was made from the CT by a radiologist and independently confirmed by the responsible neurosurgeon. Criteria for cerebral ischemia were defined as newly occurring and persisting extensive density comparisons between grey and white matter (hypodensity) and when applicable with merging of cortical furrows. Cerebral vasospasm was diagnosed by transcranial doppler (TCD) and defined as any mean flow velocity > 120 cm/sec.

Vital parameters and intracranial pressure were recorded together with the results of the cerebral microdialysis (ICU-Pilot©, CMA Microdialysis, Sweden). The microdialysis data are presented as concentrations as measured in the microdialysate, without corrections for probe recovery rates. All data were stored in a patient documentation system (DocVue©, Hewlett-Packard, Deutschland). All electronic and manual data gathered were transferred to a table. The measurements for the first twoStatview 4.0 (SAS Institute Inc, Cary, NC, USA) was used for statistical calculations and presentation of the data was made using the mean values and standard deviations. Statistical dependence of two parameters was tested by linear regression analysis. Fisher's Z transformation was used to calculate mean values of the individual correlation coefficients. Mean value analyses, in particular ANOVA testing, were used to evaluate statistically relevant differences between the measurements of microdialysis, blood glucose and insulin or noradrenalin amounts in correlation to cerebral ischemia (group 1 no cerebral ischemia, group 2 with cerebral ischemia). The significance level was $p < 0.05$.

Results

A total of 13 patients (6 males and 7 females) aged 32-61 years (mean 57 ± 11 years) with cerebral microdialysis were included in the analysis (Table 1). No complications occurred in any of the patients which could be attributed to positioning of the microdialysis catheter. The average analysis time period was 6.7 ± 3.2 days.

Table 1.   Demographic data

	Patients (n = 13)
Age (years)	57 ± 11
Body weight (kg)	80 ± 16
Initial Glasgow Coma Score	6.9 ± 1.6
Hunt & Hess classification	3.7 ± 0.6
Aneurysma localization	
PICA	2
ACA/RCA	5
MCA	4
Others	2
Comorbidities	
Arterial hypertension	8
Diabetes mellitus	4
start microdialysis monitoring/ time after initial event (days)	3.6 ± 1.9
Cerebral vasospasm	4
Special features	Anisocoria on admission (n = 2) Initially unconscious (n = 1) Initial cerebral edema CT (n = 1)

PICA - Posterior inferior cerebellar artery
ACA - Anterior cerebral artery; RCA - right carotid artery; MCA – A. cerebri media

Detection of cerebral ischemia

During the treatment severe cerebral ischemia could be detected by CT in 8 patients. The initial average GCS in these patients was 7.5 ± 1.0, versus 6.0 ± 2.0 in patients without cerebral ischemia. The cerebral
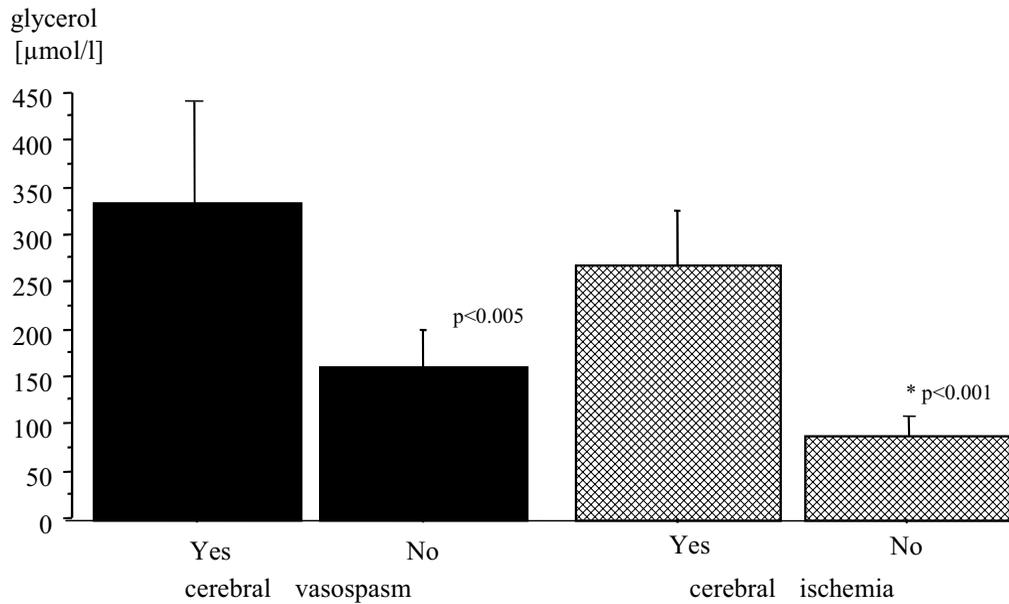
glycerol
[µmol/l]

Figure 1.   Mean concentrations for glycerol in extracellular brain tissue related to the occurrence of cerebral ischemia or cerebral vasospasm
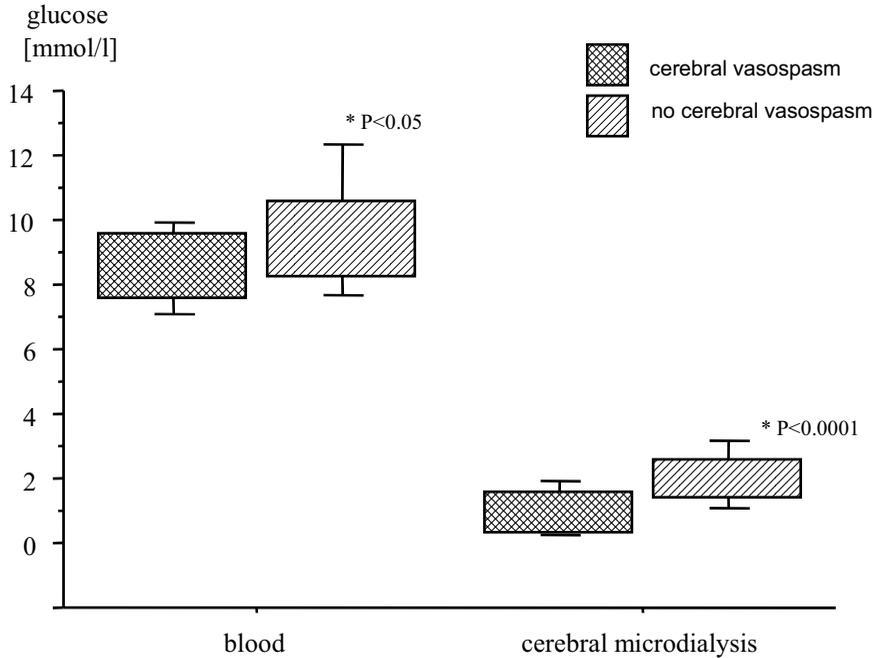
glucose
[mmol/l]

Figure 2.   Mean glucose concentrations in blood and extracellular brain tissue in patients with cerebral vasospasm

perfusion pressure (CPP) was not significantly different for the patient populations (without cerebral ischemia: 80 ± 10 mmHg vs. with cerebal ischemia 83 ± 6 mmHg).

The average blood glucose concentration for patients without cerebral ischemia was 10.0 ± 2.0 mmol/l and in the microdialysate 2.2 ± 1.0 mmol/l. Otherwise, in patients with cerebral ischemia the blood glucose was 9.0 ± 1.6 mmol/l ($p < 0,05$) and in the microdialysate 1.6 ± 1.0 mmol/l ($p < 0.05$).

Patients with cerebral ischemia showed significantly higher lactate values in extracellular brain tissue than patients without cerebral ischemia (2.4 ± 0.9 mmol/l versus 3.3 ± 1.3 mmol/l, $p < 0,005$). A tendency towards a weak correlation between blood and extracellular glucose could be detected independent of the presence of cerebra ischemia (group 1: $R^2 = 0.210$ versus group 2: $R^2 = 0.531$). The average glycerol concentrations for the microdialysate values between both groups were significantly higher for patients with ischemia (264.9 ± 215.3 µmol/l) than for the reference group (84.6 ± 58.7 µmol/l, $p < 0.0001$, Fig. 1). Glutamate values were very heterogeneous so that differences between the groups could not be analyzed (17.6 ± 65.7 µmol/l versus 12.9 ± 18.4 µmol/l).

Cerebral vasospasm

Similar results were found for the correlation between extracellular glucose and lactate in relation to the occurrence of cerebral vasospasm (without vasospasm $R^2 = 0.439$, with vasospasm $R^2 = 0.117$). The concentrations for glycerol microdialysis values between the 2 groups were significantly higher for the group with vasospasm (mean 334 ± 233.2 µmol/l) than the reference group (159.3 ± 63.6 µmol/l, $p < 0.005$) (Fig. 2). Glutamate showed a large heterogeneity so that differences between the groups could not be analyzed (without vasospasm 1.7 ± 10.1 µmol/l, with vasospasm 17.2 ± 16.2 µmol/l). The daily infusions of glucose and fat, as well as insulin and noradrenalin had no influence on these alterations.

Systemic interactions

The average blood glucose concentration during the whole measurement period was 9.4 ± 1.8 mmol/l, whereby a hyperglycemic constellation was predominant (blood glucose > 6.6 mmol/l). Temporary hypoglycemia (blood glucose < 3.3 mmol/l) occurred in 2 patients in group 1 and 5 patients in group 2. The mean extracellular glucose concentrations were 1.8 ± 1.0 mmol/l (range 0.01-6.0 mmol/l). In 4 patients from group 2 extracellular glucose concentrations < 1.0 mmol/l occurred during treatment with normal systemic glycemia.

Regression analysis between the individual blood glucose concentrations and the corresponding glucose concentrations in the microdialysate over the total observation time revealed a coefficient of determination of $R^2 = 0.220$ ($p < 0.05$). Further statistical analyis with respect to the influence of secondary events showed a weak tendency to a correlation between blood and extracellular glucose in patients without ischemia (group 1 $R^2 = 0.383$, group 2 $R^2 = 0.146$) or cerebral vasospasm (group 1 $R^2 = 0.327$, group 2 $R^2 = 0.114$).

Anaylsis of the daily insulin dosage gave a lower dosage in patients with cerebral ischemia (67.8 ± 64.2 I.E. versus 81.9 ± 64.0 I.E., not significant) or vasospasm (63.1 ± 36.1 versus 98.0 ± 62.6 I.E., $p < 0.05$), but no direct correlation to blood glucose levels ($R^2 = 0.203$), brain tissue glucose ($R^2 = 0.138$) or daily glucose ($R^2 = 0.035$) and lipid infusions ($R^2 = 0.034$).

The average daily dosage of noradrenalin was higher in patients with cerebral ischemia (6.8 ± 16.2 mg) than those in group 1 (4.3 ± 6.1 mg, not significant) so that the target of a CPP > 70 mmHg could be achieved in both groups (80.0 ± 10.0 mmHg versus 83.0 ± 6.0 mmHg, not significant). The administration of further catecholamines was of subordinate importance from clinical and statistical viewpoints. Patients where administration of noradrenalin was necessary had on average a higher blood glucose concentration (without 8.9 ± 1.2 mmol/l, with 9.9 ± 2.2 mmol/l, $p < 0.05$) which was accompanied by a higher insulin administration (without 45.6 ± 43.9 I.E./die, with 112.4 ± 67.2 I.E./die, $p < 0.0001$). The glucose levels in extracellular brain tissue showed a tendency to be higher as long as noradrenalin was applied but this was not statistically significant (without 1.6 ± 0.9 mmol/l, with 1.9 ± 1.0 mmol/l). The administration of noradrenalin had no influence on the extracellular lactate levels (without 2.9 ± 0.9 mmol/l, with 3.0 ± 1.6 mmol/l). The appearance of cerebral ischemia and vasospasm did not lead to any further significant changes.

Discussion

In this study the main question to be answered

was to what extent existing or administered energy substrates or the administration of metabolically effective medications, significantly influence cerebral metabolism and must therefore be taken into consideration for the interpretation of the results of cerebral microdialysis. In order to test the set-up used for the complex clinical picture of aneurysmal subarachnoid hemorrhaging, the typical symptoms of secondary cerebral ischemia vasospasm were correlated to each other. The results can be summarized as follows:

1. Cerebral microdialysis is suitable to detect secondary cerebral ischemia and/or cerebral vasospasm.
2. A weak statistical correlation exists between glucose in the microdialysate and the systemic glucose concentration in patients without cerebral ischemia or cerebral vasospasm.
3. Administration of noradrenalin caused a higher blood glucose concentration with corresponding higher administration of daily insulin dosages. No influence on the glucose and lactate concentrations in extracellular brain tissue was found even in correlation to secondary cerebral ischemia.
4. Administration of glucose or lipid during nutritional therapy had no influence on systemic and local metabolic parameters or insulin therapy.

The chronological behavioral pattern of glucose and lactate in the microdialysate has already been investigated in several clinical studies in patients with severe head injuries. Normally the glucose concentration in brain tissue decreased by cerebral ischemia and lactate rises [18,19]. Other investigations also found this metabolic behavior pattern in patients with aneurysmal subarachnoid hemorrhage as long as an acute cerebral ischemia could also be identified in these patients [20,21].

The results of our study also show a reduction of extracellular glucose levels with cerebral ischemia and a significant increase in lactate in the extracellular microdialysate. However, in patients with cerebral vasospasm there was a significant reduction of extracellular glucose in brain tissue which did not influence the parameter lactate.

There are a variety of explanations for this. The first hypothesis would be a lower substrate availability due to reduced cerebral blood flow with subsequent reduced concentration in the extracellular fluid, independent of the systemic supply.

Furthermore there is an unequal balance between available oxygen and local needs, for example in the

acute period of severe neuronal damage or during cerebral ischemia. This relative deficite of oxygen leads to the increased anaerobic glycolysis. Because the net energy yield is substantially less than for oxidative phosphorylation, an increased consumption of glucose to cover the energy needs could be sufficient to explain the lower $glucose_{ti}$ level. The simultaneous increase in lactate levels in the extracellular space in the subgroup with ischemia would also be explained by this. In addition glutamate would also be released due to the primary brain damage. In connection with this and also taking the results of Magistretti and Pellerin into account, it could be concluded that after activation by glutamate, glucose metabolism occurs as far as lactate also in astrocytes independent of the oxygen supply [22,23]. The lactate produced then becomes available to neurons as substrate.

As a consequence of the cerebral ischemia destruction of cell membranes and release of glycerol occurs as indirect characteristics for membrane damage [24]. The patients in the ischemia group of this study showed substantially higher values of glycerol than those in the control group. $Glycerol_{ti}$ therefore seems to be a very promising marker especially for the presence of ischemia with cell membrane destruction but not for early recognition of ischemia [25]. In the results of Peerdemann et al. a level of 150 mmol/l is described for estimation of the outcome in patients with brain trauma [26]. The mean values for $glycerol_{ti}$ in our study were clearly higher in the ischemia group. In addition to release of glycerol the transport of systemically supplied glycerol across a disrupted blood-brain barrier could also be responsible for the increase. Hillered et al. determined glycerol in plasma and brain tissue inpatients with brain damage but their results do not support this possibility [24].

Importance of systemic factors

A number of studies have shown that the presence of increased blood glucose in patients during intensive care is associated with an increased morbidity and mortality. Most of these patients had no history of diabetes and the blood glucose levels increased during the severe stress situation. In 2001 van den Berghe et al. were the first to report on the positive effect of strict control of blood glucose on patient outcome in a general surgery intensive care [10]. Subsequent studies by other groups could not, however, substantiate this effect and the intensified insulin therapy was more often associated

with a frequent occurrence of hypoglycemic events. In the meantime two large multicenter clinical studies have been carried out but no advantage of complete normalization of blood sugar in intensive care patients could be recognized in the results.

Of these two studies, one was prematurely abandoned due to the frequent occurrence of severe hypoglycemia. The attempt to maintain the blood glucose level completely within the normal range seems to have had a more negative effect in this situation. The results of this NICE-SUGAR study show the advantage of blood sugar adjustment in the range 144-180 mg/dl (8.0-10.1 mmol/l) in the patient group with "conventional" treatment compared to a group with stricter blood glucose control between 81 and 108 mg/dl (4.5-6.0 mmol/l) [27]. In the first case (conventional adjustment) 69% of patients in intensive care needed insulin whereas 97.2% of those patients with stricter adjustment criteria needed insulin. It is not surprising that even with a careful monitoring regime in the normally adjusted second group many more instances of severe hypoglycemia occurred than in the group with conventional treatment.

In a further analysis van den Berghe et al. could show an advantage by the use of intensified insulin therapy particularly for patients with isolated severe neuronal damage, whereby this was primarily limited to a critical illness polyneuropathy [28]. The demonstrated positive effect on the intracranial pressure (ICP) is only of statistical relevance with a reduction to 11 mmHg versus 13 mmHg with nearly identical CPP (81 mmHg versus 80 mmHg) and the very heterogeneous patient collective. The negative influence of hypoglycemia alone on the neurological outcome is also not unexpected. Patients in hypoglycemic shock show, for instance, an altered EEG pattern and disturbed sense of perception (cognitive function) up to loss of consciousness. At the cellular level this is often correlated to neuronal cell destruction especially in very vulnerable regions of the brain (e.g. hippocampus) [29]. In contrast animal experiments have shown that cell damage is potentiated by hyperglycemia occurring during cerebral ischemia [30]. It is therefore logical to analyse to what extent systemic supply of energy sources or medications which intervene in energy metabolism influence the substrates in brain tissue.

The results showed no direct statistical correlation between the blood glucose and the glucose measured in extracellular tissue. There was a tendency towards a stronger statistical correlation in the group with no secondary events. The data of our study were not based on a protocol of intensified insulin therapy, which can explain the increased incidence of hyperglycemic situations. However, an unexpected hypoglycemia occurred in 7 patients. A direct dependence of glucose in brain tissue on the availability of systemic glucose could be proven in healthy patients [31]. The occurrence of severe neuronal damage with a without cerebral ischemia then possibly led to a disruption of glucose production (flow-metabolism mismatch) and the glucose transport system (GLUT1 und GLUT3) [32].

Cerebral microdialysis is an established bed-side method to register alterations in cerebral metabolism. There are only a limited number of clinical studies analyzing the possible influence of systemic changes in homeostasis on the metabolic parameters measured with cerebral microdialysis. In a clinical study on 149 patients with SAH Sarrafzadeh et al. showed that the occurrence of hyperglycemia (> 120 mg/dL) within the first 7 days was a negative predictive factor for patient outcome [33]. Bilotta et al. showed that strict blood sugar control led to a reduction in the infection rate from 42% to 27% in patients with aneurysmal subarachnoid hemorrhaging, however, no influence on the neurological outcome and mortality could be demonstrated [34].

Another detailed analysis by Vespa et al. described the chronological alterations of extracellular glucose and lactate in brain tissue in patients with severe neuronal damage and the influence of systemic noxious substances. The authors found a weak correlation between extracellular glucose in brain tissue and the blood glucose concentration (r = 0.26). In 72% of the cases the reasons for lower extracellular blood concentrations were unknown. Critical alterations in cerebral perfusion led to a temporary reduction in extracellular glucose with moderate increases in extracellular lactate. A significant correlation between the two parameters could not be demonstrated (r = -0.06). A lower glucose concentration (< 0.2 mmol/l) with no connection to systemic hypoglycemia or obvious secondary brain damage was associated with a poorer outcome 6 months after onset of disease. These results suggest an increased glucose turnover in the early phase of the disease [5].

Persisting glucose concentrations of < 0.1 mmol/l in extracellular brain tissue occur ultimately in periods of severe cerebral ischemia and reflect the limited

cerebral glucose supply [35,36]. In contrast increased glucose concentrations are associated with deterioration in the neurological situation, which should not be taken as a sign of severe neurological damage but that the increased glucose principally has a direct negative influence on cells.

This leads to the hypothesis that neuronal damage per se leads to the direct dependence of glucose in brain tissue on the glucose supply in blood described in healthy patients and can therefore explain the lack of correlation in the clinical studies. The upregulation of the active glucose transporter GLUT1 seems to play a substantial role here. The situation becomes complex if, for instance, a reduced glucose supply also exists by the occurrence of reduced cerebral perfusion or ischemia or if the increased metabolic demands of the brain cannot be met due to the alterations in cerebral blood flow (flow-metabolism mismatch).

The question arises how far this constellation is influenced by systemic supply of glucose. In animal experiments the infusion of a glucose solution led to an increase in glucose levels in extracellular brain tissue. However, under moderate cerebral hypoxic conditions (p_aO_2 25-30 mmHg) glucose supply leads to a tendential increase in extracellular lactate. This becomes important because under the conditions of hyperglycemia or an increased glucose concentration in brain tissue glucose is anaerobically metabolized to lactate and therefore causes local acidosis with corresponding cell toxicity. This process is not additionally influenced by the osmotic effect of an external glucose supply [37].

The administration of noradrenalin to guarantee an adequate cerebral perfusion is advantageous in comparison to other catecholamines with respect to improved cerebral oxygenation and lack of influence of cerebral autoregulation. Under physiological conditions administration of noradrenalin via activation of α-adrenergic receptors is associated with reduced insulin secretion and therefore an increased blood glucose level. Our analysis showed increased glucose concentrations in blood and extracellular tissue but there was no direct dose-dependence. A possible explanation could be alterations to the glucose transporter GLUT1. During cerebral ischemia and also hyperglycemia there is an upregulation of GLUT1 with a corresponding increase in extracellular brain tissue glucose [38]. Animal experiments have indicated a possible passive glucose transport due to a disturbed blood-brain barrier during cerebral ischemia [39].

Furthermore, the weak relationship to the presence of cerebral vasospasm is not only exexplainable by an exclusive effect of insulin himself [40].

Within these sometimes controversial discussions over a potential effect of a strict blood glucose control, the question arises how much influence the administration of insulin has on the results of cerebral microdialysis. Investigations on the calculation of the necessary insulin dose for intensified insulin therapy show that only 35% of the blood glucose concentration can be calculated. The remaining part is influenced by nonspecific factors. Studies on the direct dose-effect relationship of insulin and cerebral glucose are limited [41-43]. A current study by Schlenk et al. investigated the correlation between insulin and glucose but found a reduction of glucose concentrations in the microdialysate. However, because of the presence of a cerebral vasospasm this could not be clearly attributed to an effect of insulin [40].

The systemic administration of insulin in our analyses also had no significant influence on glucose levels in blood or extracellular brain tissue. If a negative effect of hypoglycemia or hyperglycemia can be believed, especially on the neurological outcome, then it is necessary to consider the various constellations of extracellular glucose in severe neuronal damage. From this it can be concluded that a simultaneous systemic and local glucose monitoring is necessary as are further studies.

Furthermore, in our study no evidence of an influence of the systemic supply of triglycerides on the glycerol levels in the extracellular space was found. If the amounts of triglycerides administered enterally and parenterally as well as the hypnotics administered for sedation are calculated, the values for our patients lie within the recommended amounts for critically ill patients. Our investigations therefore confirm the investigations of Hillered et al. on acute brain damage in humans that no correlation exists between the systemic triglyceride values and those in brain tissue dialysates [24].

Summary

Monitoring of cerebral metabolism using cerebral microdialysis has proven to be a valuable instrument for differentiated surveillance of intensive care patients with severe neurological damage. The parameter glucose has become the center of interest together with the

discussion on the effectiveness of a strict blood sugar control in intensive care patients. The neurological outcome can also be influenced by a strict glucose management. The lack of a statistical correlation between glucose values in blood and extracellular brain tissue, especially during the phases of cerebral ischemia but also specific event-related behavioral patterns of metabolic parameters show the necessity for simultaneous monitoring of glucose levels in blood and brain tissue. In our investigations the systemic supply of energy suppliers, as well as noradrenalin and insulin during parenteral nutrition, did not lead to a relevant influence on the results of cerebral microdialysis.

However, the limited amount of data and the very complex pathology of the disease from a neurological perspective, necessitate further studies using microdialysis.

Correspondence address:
Jens Soukup
Department of Anesthesia, Critical Care and Palliative Care,
Carl-Thiem Hospital
Thiemstr. 111; 03048 Cottbus, Germany
☎ +49-355-46 2420
🖃 j.soukup@ctk.de

Konflikt interesów / Conflict of interest
Brak/None

Piśmiennictwo

1. Pakarinen S. Incidence, aetiology, and prognosis of primary subarachnoid haemorrhage. A study based on 589 cases diagnosed in a defined urban population during a defined period. Acta Neurol Scand 1967;43(Suppl 29):1-28.
2. Bederson JB, Levy AL, Ding WH, Kahn R, DiPerna CA, Jenkins AL, 3rd, et al. Acute vasoconstriction after subarachnoid hemorrhage. Neurosurgery 1998;42:352-60; discussion: 360-2.
3. Nordstrom CH. Assessment of critical thresholds for cerebral perfusion pressure by performing bedside monitoring of cerebral energy metabolism. Neurosurg Focus 2003;15:E5.
4. Soukup J, Zauner A, Doppenberg EM, Menzel M, Gilman C, Bullock R, et al. Relationship between brain temperature, brain chemistry and oxygen delivery after severe human head injury: the effect of mild hypothermia. Neurol Res 2002;24:161-8.
5. Vespa PM, McArthur D, O'Phelan K, Glenn T, Etchepare M, Kelly D, et al. Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. J Cereb Blood Flow Metab 2003;23:865-77.
6. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.
7. Eastman DK, Bottenberg MM, Hegge KA, Ourth H, Kabadi U. Intensive insulin therapy in critical care settings. Curr Clin Pharmacol 2009;4:71-7.
8. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978-82.
9. Van den Berghe G. Insulin therapy for the critically ill patient. Clin Cornerstone 2003;5: 56-63.
10. Van den Berghe G. The neuroendocrine response to stress is a dynamic process. Best Pract Res Clin Endocrinol Metab 2001;15:405-19.
11. Van den Berghe G, Bouillon R, Mesotten D. Glucose control in critically ill patients. N Engl J Med 2009;361: 89; author reply 91-2.
12. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180: 821-7.
13. Nordstrom CH. Cerebral energy metabolism and microdialysis in neurocritical care. Childs Nerv Syst 26: 465-72.
14. Meybohm P, Cavus E, Bein B, Steinfath M, Weber B, Scholz J, et al. Neurochemical monitoring using intracerebral microdialysis during systemic haemorrhage. Acta Neurochir (Wien) 2007;149:691-8.
15. Nordstrom CH, Reinstrup P, Xu W, Gardenfors A, Ungerstedt U. Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. Anesthesiology 2003;98:809-14.
16. Sarrafzadeh AS, Sakowitz OW, Kiening KL, Benndorf G, Lanksch WR, Unterberg AW. Bedside microdialysis: a tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? Crit Care Med 2002;30:1062-70.

17. Nilsson OG, Brandt L, Ungerstedt U, Saveland H. Bedside detection of brain ischemia using intracerebral microdialysis: subarachnoid hemorrhage and delayed ischemic deterioration. Neurosurgery 1999;45:1176-84; discussion 1184-5.
18. Alessandri B, Doppenberg E, Bullock R, Woodward J, Choi S, Koura S, et al. Glucose and lactate metabolism after severe human head injury: influence of excitatory neurotransmitters and injury type. Acta Neurochir Suppl 1999;75:21-4.
19. Valadka AB, Goodman JC, Gopinath SP, Uzura M, Robertson CS. Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. J Neurotrauma 1998;15:509-19.
20. Sarrafzadeh A, Haux D, Plotkin M, Ludemann L, Amthauer H, Unterberg A. Bedside microdialysis reflects dysfunction of cerebral energy metabolism in patients with aneurysmal subarachnoid hemorrhage as confirmed by 15 O-H2 O-PET and 18 F-FDG-PET. J Neuroradiol 2005;32:348-51.
21. Sarrafzadeh AS, Haux D, Ludemann L, Amthauer H, Plotkin M, Kuchler I, et al. Cerebral ischemia in aneurysmal subarachnoid hemorrhage: a correlative microdialysis-PET study. Stroke 2004;35:638-43.
22. Magistretti PJ, Pellerin L. Metabolic coupling during activation. A cellular view. Adv Exp Med Biol 1997;413:161-6.
23. Pellerin L, Magistretti PJ. Excitatory amino acids stimulate aerobic glycolysis in astrocytes via an activation of the Na+/K+ ATPase. Dev Neurosci 1996;18:336-42.
24. Hillered L, Valtysson J, Enblad P, Persson L. Interstitial glycerol as a marker for membrane phospholipid degradation in the acutely injured human brain. J Neurol Neurosurg Psychiatry 1998;64:486-91.
25. Marklund N, Salci K, Lewen A, Hillered L. Glycerol as a marker for post-traumatic membrane phospholipid degradation in rat brain. Neuroreport 1997;8:1457-61.
26. Peerdeman SM, Girbes AR, Polderman KH, Vandertop WP. Changes in cerebral interstitial glycerol concentration in head-injured patients; correlation with secondary events. Intensive Care Med 2003;29:1825-8.
27. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.
28. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005;64:1348-53.
29. Abdelmalik PA, Shannon P, Yiu A, Liang P, Adamchik Y, Weisspapir M, et al. Hypoglycemic seizures during transient hypoglycemia exacerbate hippocampal dysfunction. Neurobiol Dis 2007;26:646-60.
30. Cherian L, Goodman JC, Robertson CS. Hyperglycemia increases brain injury caused by secondary ischemia after cortical impact injury in rats. Crit Care Med 1997;25:1378-83.
31. Suh SW, Hamby AM, Swanson RA. Hypoglycemia, brain energetics, and hypoglycemic neuronal death. Glia 2007;55:1280-6.
32. Vannucci SJ, Maher F, Simpson IA. Glucose transporter proteins in brain: delivery of glucose to neurons and glia. Glia 1997;21:2-21.
33. Sarrafzadeh A, Haux D, Kuchler I, Lanksch WR, Unterberg AW. Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolism to outcome. J Neurosurg 2004;100:400-6.
34. Bilotta F, Spinelli A, Giovannini F, Doronzio A, Delfini R, Rosa G. The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: a randomized prospective pilot trial. J Neurosurg Anesthesiol 2007;19:156-60.
35. Landolt H, Langemann H, Mendelowitsch A, Gratzl O. Neurochemical monitoring and on-line pH measurements using brain microdialysis in patients in intensive care. Acta Neurochir Suppl (Wien) 1994;60:475-8.
36. Unterberg AW, Sakowitz OW, Sarrafzadeh AS, Benndorf G, Lanksch WR. Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. J Neurosurg 2001;94:740-9.
37. Harada M, Sawa T, Okuda C, Matsuda T, Tanaka Y. Effects of glucose load on brain extracellular lactate concentration in conscious rats using a microdialysis technique. Horm Metab Res 1993;25:560-3.
38. McDermott E, de Silva P. Impaired neuronal glucose uptake in pathogenesis of schizophrenia - can GLUT 1 and GLUT 3 deficits explain imaging, post-mortem and pharmacological findings? Med Hypotheses 2005;65:1076-81.
39. Qutub AA, Hunt CA. Glucose transport to the brain: a systems model. Brain Res Brain Res Rev 2005;49: 595-617.
40. Schlenk F, Vajkoczy P, Sarrafzadeh A. Inpatient hyperglycemia following aneurysmal subarachnoid hemorrhage: relation to cerebral metabolism and outcome. Neurocrit Care 2009;11:56-63.
41. Brunkhorst FM, Wahl HG. Blood glucose measurements in the critically ill: more than just a blood draw. Crit Care 2006;10:178.
42. Schlenk F, Graetz D, Nagel A, Schmidt M, Sarrafzadeh AS. Insulin-related decrease in cerebral glucose despite normoglycemia in aneurysmal subarachnoid hemorrhage. Crit Care 2008;12: R9.
43. Vespa P, Boonyaputthikul R, McArthur DL, Miller C, Etchepare M, Bergsneider M, et al. Intensive insulin therapy reduces microdialysis glucose values without altering glucose utilization or improving the lactate/pyruvate ratio after traumatic brain injury. Crit Care Med 2006;34:850-6.