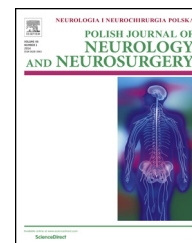


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Original research article

Regional cerebral blood flow and cellular environment in subarachnoid hemorrhage: A thermal doppler flowmetry and microdialysis study



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ARTICLE INFO

Article history:

Received 7 February 2016

Accepted 9 November 2016

Available online 18 November 2016

Keywords:

Cerebral blood flow

K coefficient

Microdialysis

Subarachnoid hemorrhage

Thermal conductivity

Brain water content

ABSTRACT

Background: Cerebral microdialysis enables assessment of regional metabolic physiology and provides biomarkers for clinical correlation in critical conditions, such as subarachnoid hemorrhage (SAH). The aim of our current study was to investigate the correlation between regional cerebral blood flow and microdialysis parameters (glucose, lactate, glycerol, pyruvate concentrations, and lactate/pyruvate metabolic ratio) in patients with SAH.

Materials and methods: Twenty-one patients with SAH were enrolled in our retrospective study. Cerebral blood flow (CBF) based on thermal diffusion methodology, the thermal coefficient K, and microdialysis biochemical markers were recorded. The duration of the brain monitoring was 10 days.

Results: Microdialysis glucose concentration was inversely related to the cerebral temperature and to the L/P ratio. Furthermore, it was positively correlated to all other microdialysis parameters but glycerol. The K coefficient was strongly and positively correlated with the temperature and marginally with the CBF. The L/P ratio was positively correlated with glycerol, while it was inversely correlated with the CBF. Patients who died had elevated L/P ratio and K coefficient compared to the survivors in our series.

Conclusions: Thermal conductivity coefficient may change over time as cerebral injury progresses and tissue properties alter. These alterations were found to be associated with the microdialysis metabolite concentrations and the CBF itself. The microdialysis biochemical indices of cell stress and death (glycerol, L/P ratio) were positively related to each other, while the measured L/P metabolic ratio was higher among patients who died.

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<http://dx.doi.org/10.1016/j.pjnns.2016.11.002>

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1. Introduction

Subarachnoid hemorrhage (SAH) accounts for 3% of all strokes, and 5% of all stroke deaths [1]. It is estimated that over 25% of potential life years lost secondary to stroke, may be attributed to SAH [2]. Despite the great advances in the diagnosis of SAH, mortality remains high (around 50%), while approximately one third of survivors have an unfavorable neurological and functional outcome [3]. Monitoring of cellular environment's events has unveiled critical biochemical processes, and has helped in predicting cerebral vasospasm, thus allowing early intervention [4–6]. It is estimated that approximately 70% of the patients with aneurysmal SAH develop angiographic vasospasm, while extracellular alterations in glutamate, lactate, lactate/pyruvate ratio, and glycerol concentrations have been associated with delayed cerebral ischemia following aSAH [4–6]. Microdialysis monitoring enables assessment of regional cerebral metabolic physiology, and provides biomarkers for clinical correlation [7,8]. Most available data in the pertinent literature come from traumatic brain injury (TBI) patients, however its utilization in the setting of aSAH has also been demonstrated [9].

The purpose of our present study was to investigate the correlation between cerebral blood flow and microdialysis parameters [glucose, lactate, glycerol, pyruvate values and lactate/pyruvate ratio (L/P)] in patients with SAH.

2. Materials and methods

All patients with CT proven diagnosis of recent onset SAH, with or without intraventricular hemorrhage (IVH), admitting Glasgow Coma Scale (GCS) score ≤ 8 , and undergoing invasive multi-parametric microdialysis monitoring were considered for enrollment in our retrospective clinical study, with prospectively set criteria. The protocol of our current study was approved by the Institutional Review Board. All the patients' data were handled according to the Helsinki and the HIPAA acts. A detailed written consent form was obtained by each patient's next of kin, for participating in our study.

Our inclusion criteria were: CT proven SAH diagnosis of recent onset (less than 24 h since symptoms started), GCS score upon admission ≤ 8 , age >18 years. Patients with age >80 years, brain dead patients, patients with impending brain death, patients with abnormal clotting studies upon admission, patients with chronic renal failure, and patients with known malignancy history were excluded from our study. Our study covered a 5-year period (from 2009 to 2013).

Complete demographic data, family and detailed past medical history of every patient were recorded at admission, followed by a thorough neurological examination.

A total of 21 patients met our inclusion criteria, out of the 37 patients admitted during the same period with the diagnosis of SAH in our institution. All patients were sedated, intubated and mechanically ventilated. A minimally invasive, multiparametric, neuromonitoring system was introduced within the first 8 h after admission to the ICU department. A frontal burr hole was placed at Kocher's point under sterile conditions, and a three way-bolt kit (Licox bolt kit, Integra

NeuroSciences, Plainsboro, NJ, USA) was inserted. This bolt kit was used for insertion of: (a) an intracranial pressure (ICP) measurement catheter (Codman microsensor kit, Codman, Johnson & Johnson, MA, USA), (b) a brain tissue-oxygen monitoring catheter (PbrO₂ measuring catheter, Licox, Integra NeuroSciences, Plainsboro, NJ, USA), and (c) a microdialysis catheter (CMA 70 Brain Microdialysis Catheter, 10 mm membrane length, 20 kDa cut off, CMA, Stockholm, Sweden). The catheters were placed in the intact brain parenchyma, and ipsilateral to the most prominent pathology area. The proper catheter position was confirmed with a brain CT scan, which was obtained within 24 h following the catheter's implantation.

A second burr hole was placed approximately 1–1.5 cm anteriorly to the previously described one, and was used for inserting a Cerebral Blood Flow (CBF) catheter (QFlow 500 Perfusion Probe, Hemedex, Cambridge, MA, USA). This catheter is flexible, biocompatible, and radio-opaque, of ~ 1 mm (3 French/19 gauge) diameter, which is inserted into the brain parenchyma for measuring regional cerebral blood flow. This catheter is FDA approved for cerebral monitoring for up to 10-days. The distal tip of the catheter was tunneled subcutaneously and was secured with sutures, 3–4 cm distal to the entry point, as to minimize the risk of infections. The data obtained are displayed on a bedside monitoring device (Bowman Perfusion Monitor, Hemedex, Cambridge, MA, USA) on a real time basis. This monitoring system provides CBF calculations by employing a thermal diffusion methodology, as this is expressed by the following equation: $CBF = K(1/V - 1/V_0)$, where CBF is expressed in ml/100 g/min, V is the voltage gradient between the two electrodes, V_0 is the voltage gradient under zero flow, and K constitutes a constant representing the brain parenchyma thermal conductivity [10]. Additionally Brain Water Content (BWC) data can be extrapolated from the measurements. In our study BWC data were provided by the Hemedex Company (Hemedex, Cambridge, MA, USA).

The duration of this multi-parametric brain monitoring was 10 days in all of our patients. After this period the catheters were removed. In those patients that there was indication for further ICP monitoring, this was performed by inserting a new intraparenchymal ICP fiberoptic catheter. All the obtained data, including ICP, brain temperature, concentrations of lactate, pyruvate, glucose, glycerol, and the L/P ratio, as well as the CBF measurements, and the K coefficient were recorded and analyzed. Moreover, the Simplified Acute Physiology Score II (SAPS II), and the Predicted Death Rate (PDR) scores were calculated and recorded.

All patients were treated using a cerebral perfusion pressure (CPP) guided protocol. The patients' outcome was evaluated with the Glasgow Outcome Scale (GOS) score at discharge, and then at 3 and 6 months post-discharge, via either a detailed neurological examination in our outpatient clinic, or via a telephone interview performed by one of the residents of our neurosurgery department.

2.1. Statistical analysis

The statistical analysis was performed using the program SPSS 22.0v. (Statistical Package for Social Sciences, IBM, Chicago, IL,

Table 1 – Demographic characteristics, SAPS II, and PDR scores of our patients.

Variable		N (%)	Mean ± Std. deviation
Gender	Female	7 (33.3)	
	Male	14 (66.6)	
Outcome	Death	8 (38.1%)	
	Survival	13 (61.9)	
Operations performed	Clipping	6 (28.6)	
	Coiling	4 (19.0)	
	Craniectomy (decompressive)	8 (38.1)	
	Ventricular drain	15 (71.4)	
Modified Fisher scale	Grade 3	6 (28.6)	
	Grade 4	15 (71.4)	
Mortality	Brain death	5 (23.8)	
	-Rebleeding	3 (14.3)	
	-Brain stem herniation due to edema	2 (9.5)	
	Multi-organ failure (due to sepsis)	3 (14.3)	
Age			48.05 ± 15.9
SAPS II			51.14 ± 14.13
PDR			49.60 ± 24.96

USA). Data were extracted to modified Excel spreadsheet files, and then were transferred to SPSS for further processing. Normality was checked by Shapiro–Wilk test. Student's t test was used for comparisons between groups. Generalized Estimating Equations (GEE) was applied to continuous variables in order to handle repeated observations within subjects. Repeated, real time, Hemedex values were analyzed on hourly intervals, in accordance to microdialysis data. Statistical significance was set at $p = 0.05$.

3. Results

Our study population comprised of 21 patients (14 males and 7 females). The mean age was 48.05 ± 15.93 years, while their age spectrum was 18–73 years. The observed mortality rate in our series was 38% (8/21 patients) (Table 1). Calculated SAPS II were 51.14 ± 14.12 , while the PDR scores were 49.60 ± 24.96 (Table 1).

Fourteen patients underwent brain surgery [clipping: 8 out of 21 (38.1%), coiling: 4 out of 21 (19.0%)]. Eight patients underwent craniectomy while fifteen patients were subjected to ventriculostomy as well. Five of the patients died because of the primary neurological insult (brain death preceded) while two of them suffered a fatal rebleeding incident. The cause of mortality for the remaining three patients was multiorgan failure because of sepsis. All patients were classified as grade 3 or 4 on the modified Fisher scale (Thick focal or diffuse SAH with or without IVH).¹

Regarding our multiparametric monitoring parameters, none the differences observed reached the levels of statistical significance. The intraparenchymal cerebral temperature was found to be higher in survivors than in patients who died (36.83°C vs. 36.48°C , $p = 0.248$). Likewise, CBF was also observed to be higher in survivors than in patients who died (33.66 vs. 29.34 ml/100 g/min, $p = 0.495$). Additionally, lactate

values were found to be higher in survivors than in patients who did not survive (8.52 vs. 5.89 mmol/lit, $p = 0.498$). Contrariwise, glucose, glycerol and pyruvate were found in higher concentrations in non-survivors compared to patients who survived (1.18 vs. 0.99 mmol/lit, 122.92 vs. 92.29 $\mu\text{mol/lit}$, and 124.47 vs. 112.06 $\mu\text{mol/lit}$; $p = 0.414$, $p = 0.488$ and $p = 0.348$, respectively). The largest differences were observed in the L/P ratio, and the K coefficient. In particular, patients who died had an elevated L/P ratio and K coefficient in comparison with the survivors (L/P: 50.01 ± 24.79 vs. 39.36 ± 9.57 , $p = 0.176$; K: 3.34 ± 0.69 vs. 3.02 ± 0.35 , $p = 0.167$ respectively). Regarding Brain Water Content, only two patients had a mean BWC lower than 70.2% which is considered within the normal range [11].

Further analysis of our dataset demonstrated that glucose was inversely related to the cerebral temperature and to the L/P ratio, while it was positively correlated to the K coefficient, the CBF, and all the microdialysis parameters with the exception of glycerol. The observed concentrations of glycerol, and the lactate were inversely correlated with the obtained CBF measurements. The L/P ratio was positively correlated with glycerol, and inversely correlated with CBF (Table 2). When the GEE model was applied to K estimation, the K coefficient was correlated with glucose, pyruvate, marginally and positively to CBF, while it was strongly and positively correlated with the cerebral temperature (Table 3). CBF was inversely related to BWC ($r = -0.086$, $p < 0.001$).

4. Discussion

Analysis of our current results demonstrated that the microdialysis biochemical indices of cell stress and death (glycerol, L/P) were positively related to each other, while the observed L/P metabolic ratio was higher among patients who died. The unfavorable prognosis in patients with high L/P ratio and low CBF is well documented in the literature. In the study by Bouzat et al., comatose patients demonstrated significantly higher average L/P ratios ($p < 0.02$) [7]. In the same study, low regional cerebral blood flow correlated with increased intracranial pressure (higher than 20 mm Hg), brain tissue PO_2 less

¹ Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, MacDonald RL, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. *Neurosurgery*. 2006;59(1):21-7.

Table 2 – Correlation between cerebral blood flow and the microdialysis measured cerebral parameters.

		Pyr	Glyc	Lac	CBF	K	T	L/P
Glu	r	0.382**	–0.007	0.179**	0.117**	0.140**	–0.219**	–0.068**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
Pyr	r		0.178**	0.637**	0.180**	–0.160**	–0.428**	–0.099**
	p		0.019	<0.001	<0.001	<0.001	<0.001	<0.001
Glyc	r			0.587**	–0.134**	–0.009	–0.130**	0.447**
	p			<0.001	<0.001	0.567	<0.001	<0.001
Lac	r				–0.026	0.016	–0.269**	0.464**
	p				0.112	0.330	<0.001	<0.001
CBF	r					0.235**	0.198**	–0.047**
	p					<0.001	<0.001	0.003
K	r						0.545**	0.104**
	p						<0.001	<0.001
T	r							0.002
	p							0.878

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Glu: glucose; Pyr: pyruvate; Glyc: glycerol; Lac: lactate; CBF: cerebral blood flow.

L/P: lactate/pyruvate ratio; T: temperature; K: coefficient (thermal conductivity).

Table 3 – GEE model for K coefficient.

Parameter	B	95% Wald confidence interval		p	Exp(B)	95% Wald confidence interval for Exp(B)	
		Lower	Upper			Lower	Upper
(Intercept)	–87.264	–137.577	–36.950	0.001	1.264E–38	1.782E–60	8.968E–17
Glycerol	–0.004	–0.014	0.006	0.458	0.996	0.986	1.006
Pyruvate	–0.044	–0.086	–0.003	0.037	0.957	0.917	0.997
Lactate	1.188	–0.081	2.458	0.067	3.282	0.922	11.681
L/P	–0.006	–0.034	0.021	0.647	0.994	0.966	1.021
Glucose	3.294	0.904	5.684	0.007	26.943	2.469	294.058
Temp	2.967	1.627	4.306	<0.001	19.425	5.090	74.135
CBF	0.108	0.002	0.214	0.046	1.114	1.002	1.239

Dependent variable: K.

Statistically significant associations in bold.

Model: (Intercept), glycerol, pyruvate, lactate, L/P, Glucose, temp, CBF.

than 20 mm Hg, cerebral microdialysis glucose less than 1 mmol/L, and L/P ratio more than 40 [7].

Moreover, the K coefficient (related to thermal conductivity) seems to be susceptible to changes, associated with metabolite concentrations (as these were measured by microdialysis), and even by the CBF itself. These changes were minimal in our series, but they cannot be ignored, raising thus, questions about the interpretation of CBF monitoring based on the thermal conductivity. Tissue damage may be reflected on the K value, through changes in tissue conductivity, which further influences the CBF. The extracellular milieu of brain tissue contains ions, metabolic substrates and neuroactive compounds, which dynamically change during brain activity and tissue repairing process [12]. This content alteration can significantly influence, not only the transmission of signal information in the nervous tissue, but also tissue perfusion. These two parameters are interrelated, as neuronal tissue viability depends on the CBF [13].

Experimental data, obtained from a study in the rat brain, showed that protein synthesis begins to be inhibited at flow rates below 55 ml/100 ml/min, while lactate accumulation increase at flow rates below 35 ml/100 g/min [14]. It has been

found that CBF correlates best with glutamate, followed by glycerol, whereas the L/P ratio is affected only after longer periods of ischemia [15]. Low global CBF has been accompanied by metabolic disturbances, which were accurately determined by microdialysis [16]. It seems that a cerebral vascular event, may lead the brain to a state of persistent metabolic crisis, as this is reflected by abnormal cerebral microdialysis, which is not related to the ischemia itself [17]. Regarding the correlation between the CBF and the cerebral temperature, the mean cerebral blood flow (CBF) in patients with cerebral temperature between 36.0 °C and 37.5 °C was 37.8 ± 14.0 ml/100 g/min. The lowest CBF (17.1 ± 14.0 ml/100 g/min) has been measured in patients with a cerebral temperature <36.0 °C [18]. The linearity of correlation between the CBF and the cerebral temperature was also confirmed by our current data.

Interestingly, the results of our present study raise the issue of the interpretation of CBF calculation, as the K coefficient appears to be fluctuating. The observed K fluctuation depends on the brain parenchyma properties, which may alter over time, as patient's condition changes. The K coefficient represents a tissue thermal conductivity constant, which is dependent on the type of the tissue, its histological structure,

and its temperature. Although its value for a certain temperature is considered as a rather stable characteristic of mammalian tissues, and its relation to tissue content is well established, it may well change when tissue content changes. This change occurs in cerebral events, where the proportions of blood and cell membranes are dynamically and constantly rearranged.

This fact had been noticed by Ponder, who conducted experiments with canine brain, lung, liver, muscle, and blood samples, in both homogenized and en block forms [19]. It was found that high lipid content (e.g. in brain tissue) accounts for low K values, and even subtle differences in tissue consistency may result into surprisingly large changes in thermal conductivity [19]. Moreover, he reported that homogenates may show smaller K values than blocks of the same tissue, and this may be attributed to the different heat propagation patterns, which structured tissue carries. He postulated that the heat could be propagated better along structured pathways than in homogenates, where the cyto-architecture and the membranous structures have been destroyed [19]. In that context, it is possible that changes in brain architecture may cause K alterations, which in turn may affect the CBF calculation [19]. Indeed, our present study supports the idea that a linear relation between the K factor and the microdialysis-measured parameters may exist. Severe cerebral tissue damage may cause deviation of the theoretically calculated K values, used in the interpretation of the CBF. This finding may have clinical implications, especially when BWC calculations and estimation of brain edema take place.

There are confounding factors weakening the strength of our conclusions. Firstly, we did not use an imaging technique for measuring CBF such as CT perfusion or MR diffusion. In this regard, we were not able to verify the recorded fluctuations of the measured CBF with another methodology. The rather small size of our study population also affects the statistical power of our results. Furthermore, the heterogeneity of our study population does not allow definite conclusions to be drawn, especially on the kind of the relation and the mathematical equation between the K alteration and the measured CBF values. BWC has been calculated according to existing formulas. However, since only 2 of the patients had brain water content less than 70% (considered low), further analysis might have been statistically weak.

In conclusion, our current study underlines the fact that biochemical indices of cell stress and death (glycerol, L/P) are positively related to one another, while K values should not be considered as constant as previously thought, especially in patients in critical condition. Our current data clearly demonstrate that K coefficient may well change as brain damage progresses, and tissue properties alter. Furthermore, clinicians should be aware of this complex relationship between the K coefficient and the CBF measurements for accurately interpreting all the monitoring parameters and adjusting their patient management accordingly.

Conflict of interest

None declared.

Acknowledgements and financial support

We would like to thank Drs H.F. Bowman and S.D. Greenwald from Hemedex for their valuable assistance and insightful comments, as well as for providing us with the Brain Water Content calculations. We also wish to thank Dr I. Nikaina, for her valuable advice on GEE models implementation.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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