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Ischemia monitoring after aneurysmal subarachnoid haemorrhage; contribution of brain tissue oxygen and cerebral microdialysis monitoring

(Monitorage de l'ischémie après hémorragie sous-arachnoidienne; apport de l'oxygénation tissulaire et de la microdialyse cérébrale)

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Abstract

<u>Introduction</u>: Delayed cerebral ischemia (DCI) is a frequent and serious complication of aneurysmal subarachnoid haemorrhage (SAH). The diagnosis of DCI lies primarily on the deterioration of the clinical state (neurological deficit), but can be difficult to detect in the comatose patient. Transcranial Dopper (TCD) and perfusion Computer Tomography with calculation of cerebral blood flow (CBF) and brain perfusion help with the diagnosis of DCI but their predictive values remain limited. The DCI mechanisms are complex, involving alteration of CBF, impaired cerebral autoregulation, brain energy dysfunction and activation of pro-inflammatory mediators. The use of novel techniques for advanced intracranial monitoring (including brain tissue PO_2 and cerebral microdialysis) offer the opportunity to study in detail DCI physiopathology and might help detecting DCI and guiding therapeutic interventions in patients suffering from SAH.

<u>General objectives</u>: The main objective of this study was to examine the relationship between global CBF – measured with TCD and perfusion-CT – and regional brain metabolism, measured with the brain tissue oxygen ($PbtO_2$) probe and the cerebral microdialysis (CMD) technique.

<u>Specific objectives</u>:
To examine the relationship between:
- DCI and the brain tissue oxygen pressure reactivity index (ORx), which is calculated as the moving linear correlation coefficient between $PbtO_2$ and CPP (=mean arterial pressure – intracranial pressure). The ORx is considered as a surrogate marker of the cerebral autoregulation state;
- ORx and CBF, calculated with the perfusion-CT;
- ORx and CMD markers of brain energy metabolism (including the lactate/pyruvate ratio and glucose).

<u>Methods</u>: Retrospective analysis of an ongoing cohort database of patients with coma (defined by a Glasgow Coma Scale (GCS) ≤ 8) after aneurysmal SAH, with an abnormal CT-scan (Fisher grade II-IV), who underwent intracranial monitoring with $PbtO_2$ and CMD as part of standard care. Intracranial monitoring was inserted after admission (2 ±1 days). A total of 21 patients were admitted in the Intensive Care Department with poor-grade SAH and underwent imaging and aneurysm securisation (with surgical clipping or endovascular coiling). Cerebral microdialysis allows to measure every hour, through a catheter placed in the cerebral parenchyma (white matter), the extracellular concentration of the main brain metabolites (glucose, lactate, pyruvate, lactate/pyruvate ratio). The DCI is diagnosed with the TCD and the perfusion-CT. The CBF (derived from the cerebral blood volume and the mean transit time) was calculated with the perfusion-CT, with a CBF < 32ml/100g/min that was used as the threshold for brain oligemia. Brain cell hypoxia was defined as a $PbtO_2$ <20mmHg and/or a CMD lactate/pyruvate-ratio >40. The different variables were compared by univariate analysis using a Wilcoxon test for comparisons. The relationship between variables was analysed with the Pearson's R linear correlation coefficient factor.

<u>Expected results</u>: From a clinical standpoint, if a relationship between regional brain physiological variables and global cerebral blood flow can be demonstrated, this could serve as a validation of $PbtO_2$ and cerebral microdialysis monitoring as complementary tools for the diagnosis and the management of DCI in comatose SAH patients. From a pathophysiological standpoint, this study will provide new insights concerning the relationship between cerebral blood flow, brain oxygenation and cerebral energy metabolism in the acute phase of SAH.

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1   Introduction:

Symptomatic vasospasm with delayed cerebral ischemia (DCI) is a frequent complication of aneurysmal subarachnoid haemorrhage (SAH), occurring in about 30 to 70% of patients[1], and is associated with substantial morbidity and mortality[2]. Diagnosis and management of DCI remains a challenging task for clinicians.   Clinical examination is the first trigger to intervention however it is not always reliable in patients with coma after SAH. Additional diagnostic tools include perfusion CT and trans-cranial Doppler[3,4] but their predictive value remains limited[5].

Given the limited value of the available tools, additional techniques have been developed particularly for the diagnosis and the management of DCI in comatose SAH patients. These include so-called multimodal monitoring with the use of invasive intra-parenchymal brain tissue oxygen ($PbtO_2$) probes and the implementation of the cerebral microdialysis technique (see chapter 3.5 and 3.6). These tools however require further investigation and validation in the clinical setting. They offer a unique technology to better explore the complex pathophysiology of SAH and allow a surrogate marker for the assessment of cerebral blood flow (CBF) and patient cerebral autoregulatory status at the bedside.

1.1   Delayed cerebral ischemia: pathophysiology

Subarachnoid haemorrhage due to a ruptured intracerebral aneurysm causes early secondary brain injury with increased intracranial pressure, brain shift and herniation[6]. Delayed cerebral ischemia due to vasospasm is the most common and one of the most severe complications after SAH, generally occurring at 5-10 days from acute injury. The exact mechanisms of DCI after SAH are complex and still not completely understood[7,8]. Among other factors, the impairment of cerebral autoregulation has been recognized as an important pathophysiologic determinant of DCI. Like almost any other vascular beds, the brain's vasculature has the intrinsic protective ability to maintain adequate CBF relatively independent of fluctuations of systemic arterial pressure. This process is known as the cerebral pressure autoregulation or cerebro-vascular pressure reactivity. Below or above a range of vascular pressure (50 mmHg and 160 mmHg respectively) the CBF will progressively lack its ability to remain independent from the blood pressure and will passively follow the pressure changes.

After SAH, cerebral autoregulation is frequently impaired leaving the brain more susceptible to secondary ischemic insults[9–13]. Impaired cerebro-vascular pressure reactivity has been linked with DCI after SAH in clinical studies[14–16]. Monitoring of regional $PbtO_2$ gives an indirect measurement of CBF[17]. The on-line linear correlation between $PbtO_2$ and the cerebral perfusion pressure (CPP= intracranial pressure (ICP) - mean arterial pressure, MAP) is an indicator of the cerebro-vascular pressure reactivity and of the adequacy of cerebral autoregulation after SAH. This index is called the oxygen pressure reactivity index or ORx. In normal conditions CPP and $PbtO_2$ are not correlated and therefore the ORx is close to 0. In conditions of impaired autoregulation, when CBF follows passive changes of systemic pressure, $PbtO_2$ and CPP are linearly correlated (and thus the ORx is above 0.3)[18].

1.2   Hypothesis, objectives and expected values

The primary endpoint of this study was to examine the relationship of global CBF assessed with perfusion CT with regional intracranial monitoring using PbO_2 and intra-cerebral microdialysis. From a mechanistic point of view, this study will give new data concerning the relationship between cerebral blood flow, oxygenation and metabolism after SAH. From a

clinical point of view, if we demonstrate a relationship between regional physiological brain variables and global CBF, this would validate $PbtO_2$ and CMD as complementary tools for the diagnosis and management of DCI in comatose patients after SAH, in whom standard diagnostic tools are less reliable.

1.3   Study type

Retrospective analysis of a cohort database of patients admitted to the Service de Médecine Intensive Adulte (SMIA), at the Lausanne University Hospital (CHUV), Lausanne, Switzerland. The data analysis was conducted at the Neuroscience Critical Care Research Group, SMIA, CHUV, under the leadership of Mauro Oddo, MD, médecin-adjoint, PD-MER. Authorization for the study was obtained from the Clinical Research Ethical Committee at the University of Lausanne, with waiver of patient consent given the retrospective nature of the study.

1.4   Patients

Subjects were part of an ongoing cohort database of patients with coma (defined by a Glasgow Coma Scale (GCS) ≤ 8) after aneurysmal SAH with an abnormal CT-scan (Fisher grade II-IV) who underwent intracranial monitoring with ICP, $PbtO_2$ and cerebral microdialysis as part of standard care, according to a written institutional algorithm. Intracranial monitoring was inserted soon after hospital admission (2 ±1 days). A total of 21 patients were admitted in the Intensive Care Department with poor-grade SAH. Aneurysm rupture was treated with surgical clipping or endovascular coiling.

1.5   Management

Patients were treated according to the protocol for the management of SAH from the CHUV. Patients were admitted after a post-operative procedure (coiling or clipping). Patients were sedated with propofol and sufentanil, and mechanically ventilated aiming to PaO_2 90-100 mmHg and $PaCO_2$ 35-40 mmHg. Brain physiological targets were set to maintain ICP <20 mmHg, cerebral perfusion pressure (CPP=mean arterial pressure, measured via an intra-arterial catheter – ICP) > 60 mmHg, and $PbtO_2$ >20 mmHg.

The aim was the prevention and treatment of the secondary cerebral lesion and the prevention of the vasospasm responsible of the delayed cerebral ischemia. All patients received oral or intravenous nimodipine for prophylaxis of DCI. Medical therapy of DCI consisted of hemodynamic augmentation with fluids (isotonic lactate), vasopressors (norepinephrine), and inotropes (milrinone). DCI refractory to medical therapy was managed by interventional radiology with in situ infusion of vasodilators (nimodipine or milrinone) and mechanical angioplasty when required.

2 Intracranial monitoring

2.1 Brain Oxygen

PbtO$_2$ was measured using the Licox$^®$ catheter (Integra Neurosciences, Plainsboro, NJ, USA). Brain hypoxia can lead to secondary lesion. It has therefore become necessary to monitor the brain oxygen pressure to distinguish a normal and impaired oxygen supply. In the last decade, the monitoring of brain oxygen pressure has shown its clinical utility. The brain oxygen pressure is known as the arterio-venous oxygen tension difference (AVTO$_2$) times the cerebral blood flow (CBF):

$$PbtO_2 = AVTO_2 \times CBF$$

AVTO$_2$ is defined as the arterial oxygen pressure (PaO$_2$) minus the venous oxygen pressure (PvO$_2$). PbtO$_2$ represents the interaction between plasma oxygen tension and CBF[19].

There are four different ways to measure PbtO$_2$: jugular bulb oximetry, direct brain tissue oxygen tension measurement, near infrared spectroscopy and oxygen-15 positron emission tomography (PET). Attention will be given to the direct brain tissue oxygen tension measurement, as it is the technique which has been used for our patients and it is available at patient bedside.

The Licox PbtO$_2$ probe consists of a catheter that is inserted during neurosurgery and placed, for SAH patients, in the parenchymal region where vasospasm and DCI is more likely to develop, according to the location of the ruptured aneurysm localisation and the distribution of the SAH. The Licox PbtO$_2$ probe is based on the Clarke principle. Parenchymal oxygen diffuses through a membrane and is reduced at the contact of the cathode producing a voltage change. The diffusion of the oxygen is proportional to its concentration and the voltage change is proportional to the amount of reduced oxygen. This process is temperature dependent and requires constant calibration to patient body temperature.

2.2 Cerebral microdialysis

Cerebral microdialysis (CMD) is a minimally invasive technique that allows a bedside online analysis (every hour) of brain tissue biochemistry during neurointensive care. The device consists of a micro-catheter (CMA 70 catheter, M Dialysis AB$^®$, Stockholm, Sweden) that is placed in the brain parenchyma, close to ICP and PbtO$_2$ monitors. The catheter has at its tip a semi-permeable dialysis membrane through which an artificial cerebrospinal fluid is infused at a constant slow flow rate (0.3μl/min), using a controlled pump (CMA 106$^®$ pump). Several metabolites (including glucose, lactate, pyruvate, glutamate, glycerol) can be measured in patient's brain extracellular fluid through the semi-permeable membrane following a concentration gradient according to the diffusion principles (20kDa cut-off). Once at equilibrium, the fluid (dialysate) is collected and analysed at the bedside every hour using a kinetic enzymatic methodology (ISCUS flex$^®$ analyser).

All intracranial probes were inserted in the operating room by a neurosurgeon through a triple-lumen bolt (Integra Neurosciences), and placed into apparently normal brain parenchyma (sub-cortical white matter), in the right frontal lobe (see **Figure 1**)[20]. A CT scan was performed at $\approx$ 24 hours to confirm the correct placement of intracranial monitors.

Figure 1. Location of cerebral microdialysis and brain tissue PO2 catheters. One illustrative example of probe location in the right frontal subcortical white matter, with close positioning of CMD and brain tissue PO2 catheters

2.3 Calculation of the Index of Brain Tissue Oxygen Pressure Reactivity (ORx) for the Assessment of the Autoregulatory Status

The ability of the brain to maintain PbO_2 despite wide CPP changes is known as the cerebro-vascular pressure reactivity [21]. The index of $PbtO_2$ pressure reactivity (ORx) is calculated as the moving linear (Pearson's) correlation coefficient between values of CPP and $PbtO_2$ from the previous 60 minutes of monitoring[22]. The ORx is an indicator of the cerebral autoregulatory status, with values going from -1 to 1. An ORx which is close to 0 indicates a normal autoregulatory status, while a positive high ORx (>0.3) indicates an impairment of cerebro-vascular pressure reactivity and an abnormal cerebral autoregulation, where $PbtO_2$ passively follows CPP and a much higher risk of secondary cerebral ischemic insults[9] and worse outcome after TBI[18], SAH[9], and stroke[23].

The use of cerebral microdialysis has been described in TBI and SAH patients[17]. While the technique is well established in patients with traumatic brain injury, data regarding SAH patients are still relatively limited. The measure of lactate, pyruvate, lactate/pyruvate ratio combined to the partial pressure brain tissue oxygen ($PbtO_2$) readings, and glucose has been suggested to be useful to detect secondary ischemia/hypoxia due to vasospasm[24,25]. In general, high mean lactate/pyruvate ration and low glucose is correlated with ischemia and poor outcome. Others have related a high lactate without hypoxia/ischemia[26]. Data combining cerebral microdialysis with $PbtO_2$ are particularly limited: they warrant further investigation since they could help understanding the pathophysiology of SAH and might improve the management of DCI following SAH.

Brain perfusion CT was performed using a multi-detector row CT Lightspeed (GE medical systems, Milwaukee, WI, USA). Scanning was initiated 5 seconds after injection of 50 ml of iohexol (300 mg/mL of iodine; GE Healthcare), at a rate of 5 mL/sec, with the following parameters: 80 kV, 240 mAs, 0.4 rotations/sec, total duration of 50 sec. The series evaluated sixteen adjacent 5-mm-thick sections of brain parenchyma. Post-processing of PCT data was performed by two experienced neuro-radiologists, using a dedicated software (Brilliance Workspace Portal®, Philips medical systems, Cleveland, OH, USA) which employs the central volume principle using deconvolution to measure the mean transit time (MTT); cerebral blood volume (CBV) is calculated from the time-enhancement curves, and cerebral

blood flow (CBF) is derived from the equation CBF = CBV/MTT. For each PCT, one region of interest (ROI) was manually drawn around the probe (surface area ~ 50 mm^2) to calculate regional CBF, and two others ROI (one for each hemisphere) of approximately 250 mm^2 were selected above the ventricular system and included anterior and middle cerebral artery territories (global CBF), as described by Sala et al[20]. Since probes were located in the white matter, supra-ventricular ROI were drawn in areas of predominant white matter to allow concordant measurements of global supra-tentorial CBF in the same type of tissue. Calculation of global and regional CBF was performed by an experienced neuro-radiologist, blinded to intracranial monitoring data.

3 Data collection and processing

The index of PbtO$_2$ pressure reactivity (ORx) is calculated as the moving linear correlation coefficient (Pearson's *r*) between CPP and PbtO$_2$ from the previous 60 minutes of monitoring[22]. Artefacts caused by temporary disconnection of catheters or nursing interventions were manually eliminated from the data sets, and ORx was calculated after artefacts elimination.

PbtO$_2$ and ORx data were subsequently manually matched to CMD data. Brain physiologic variables were matched to perfusion CT data during the time window that we considered as the most representative of the patient brain state, *i.e.* we included samples obtained at the time of perfusion CT, plus samples from the 3 hours previous and the 3 hours following the CT time (total of 7 epochs). The same procedure was applied to match brain physiologic variables to trans-cranial Doppler (TCD) data. If data close to the perfusion CT or TCD were missing, then we extended the time-period up to maximum 3 hours for perfusion CT and 8 hours for TCD.

3.1 Statistical analysis

Data analysis was performed using JMP-10R (SAS Institute, Cary, NC, USA). A *p* value < 0.05 was considered statistically significant. Data were expressed as median interquartile range. Associations of cerebral physiologic and metabolic variables with CT results were analyzed with univariate analysis, using non-parametric Wilcoxon test for continuous variables and Chi-square test for categorical variables.

4   Results

4.1   Patients Characteristics

The studied population consisted of 21 consecutive patients with the diagnosis of poor-grade comatose aneurysmal SAH admitted in the intensive care unit (ICU) of the CHUV (Service de Médecine Intensive Adulte SMIA).

Table 1. Patients Characteristics

Age, years	57 (40-72)
Female gender, nr/total nr.	15/21
Glasgow Coma Scale	6 (3-14)
Duration of brain physiologic monitoring, hrs	133 (26-2897)
Time from SAH to monitoring, hrs	23 (5-144)
Endovascular coiling/Surgical clipping	10/11
Delayed Cerebral Ischemia (DCI)	11/21

Data are expressed as median (range).

4.2   Relationship between ORx index and DCI

Average daily ORx from day 1 to 6 of the DCI group compared to the non-DCI group are presented in **Figure 2**.
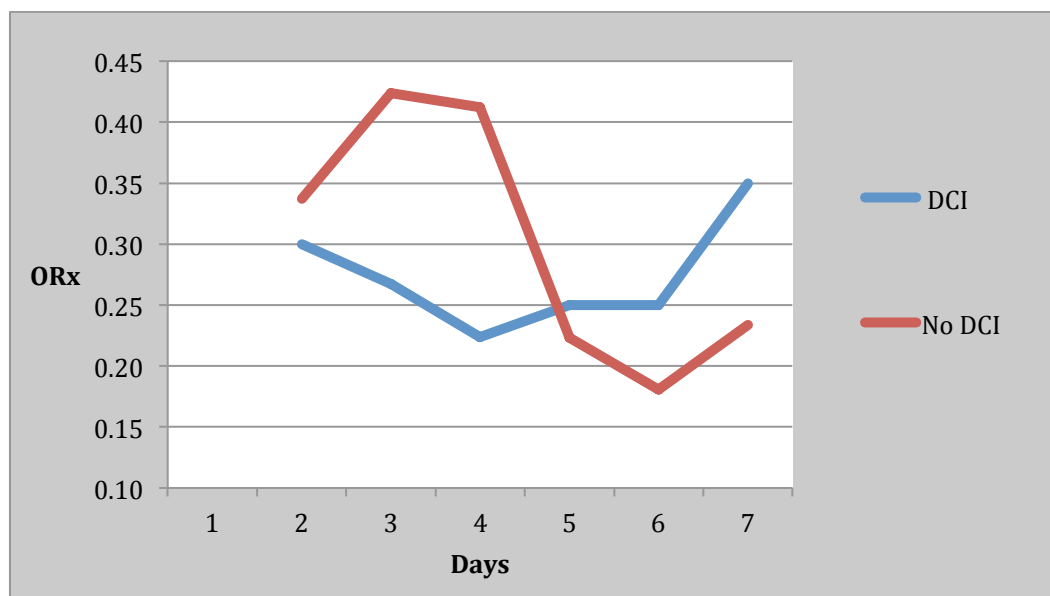
Most importantly from the clinical standpoint, ORx was high in the two subgroups in the early phase (suggesting impaired cerebro-vascular pressure reactivity in the first 24 hrs following SAH), but then tended to normalization in patients with no DCI, while it remained high and even increased in those who subsequently developed DCI (see above average daily ORx between the two subgroups; DCI n=11 vs. no-DCI n=10, **Figure 2**).

Compared to patients with no DCI (n=10), subjects with a confirmed diagnosis of DCI (n=11) had higher ORx values (median 0.34 interquartile [0.15-0.58] vs. 0.41 [0.17-0.62]; p=0.0236, see **Summary Table**).

4.3   Relationship between Cerebral Blood Flow and ORx

In order to assess the global CBF and, by extension, the presence of vasospasm, 18 perfusion-CT/angioCT among 10 patients and 31 transcranial Doppler among 9 patients were performed. The ORx values 3 hours before the exam and 3 hours after the exam were studied. We compared the ORx values for the exam that confirmed the absence/presence of a vasospasm.

4.3.1   Perfusion CT assessment of Cerebral Blood Flow

In comparison with the normal perfusion CT group, the perfusion CT group that diagnosed an oligemic CBF showed a trend towards higher ORx values (mean values: 0.5 [0.27; 0.7] vs. 0.36 [0.18; 0.63] p=0.08).

4.3.2   Trans-cranial Doppler assessment of Cerebral Blood Flow

In the same way, in comparison to the normal transcranial Doppler group, the transcranial Doppler group that diagnosed pathologically elevated CBF velocities indicative of symptomatic vasospasm showed a trend towards higher ORx values (mean values: 0.505 [0.26; 0.72] vs. 0.43 [0.2; 0.61] p=0.065).

4.4   Relation between indexes of regional cerebral autoregulation and microdialysis biomarkers

In order to study both parameters, the ORx values were matched to every single MD sampling. Attention was brought to the Lactate/Pyruvate ratio and glucose

4.4.1   Lactate Pyruvate ratio and ORx values

A LPR> 40 is often used as a threshold of cerebral hypoxia or ischemia and is associated with a poor outcome[5;6;7]. ORx values were dichotomized into >0.3 (impaired autoregulation) or <0.3 (preserved autoregulation) in order to assess the LPR level corresponding to each group. Higher LPR were found when the ORx value was >0.3 (mean values 29 [25; 34]; vs. 27 [24; 33] p=0.0930).

4.4.2   MD Glucose and ORx values

Higher ORx values were found when glucose level was below 1mM, and when the perfusion CT diagnosed vasospasm with cerebral hypoperfusion also statistically significant and clinically relevant lower cerebral glucose levels were found (mean value 1.1 [0.11; 4.38] vs. 0.79 [0.37; 2.87]; p=0.03).

4.5   Summary Table

Illustration of the differences in brain physiologic variables between patients with vs. without DCI, based on clinical, neuro-radiological and TCD findings. Results are expressed as medians (interquartile ranges).

Variable	DCI group N=11	No-DCI group N=10	P value
ORx	0.41 [0.15-0.58]	0.34 [0.17-0.62]	**0.02**
	Oligemic perfusion CT	Normal perfusion CT	
CMD Glucose	0.79 mM [0.37; 2.87]	1.1mM [0.11; 4.38]	**0.03**
ORx	0.5 [0.27; 0.7]	0.36 [0.18; 0.63]	0.08
	Positive TCD for vasospasm	Negative TCD for vasospasm	
ORx	0.505 [0.26; 0.72]	0.43 [0.2; 0.61]	0.065
	Impaired ORx>0.3	Preserved ORx<0.3	
CMD Lactate/pyruvate ratio	28.895 [24.85; 34.44]	27.91 [24.02; 32.95]	0.0930

4.6   Autoregulation 48 Hours before Vasospasm

Four patients were monitored with a $PbtO_2$ probe at the time they underwent a vasospasm. The course of the ORx values during the 48 hours before the vasospasm was rising in the four studied cases, suggesting progressive impairment of cerebro-vascular pressure reactivity over time (**Figure 3**).

ORx 48-0 Hours before vasospasm
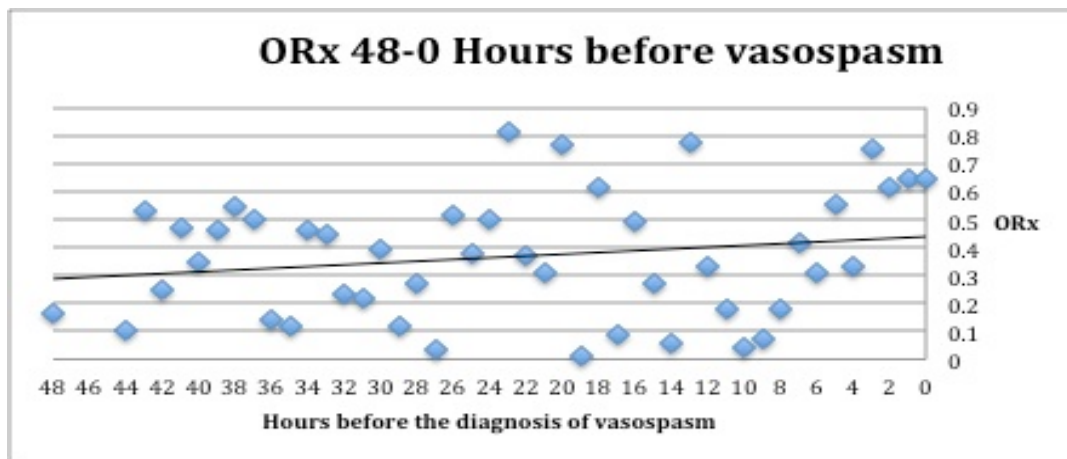
5 Discussion and conclusions

5.1 Impaired cerebrovascular autoregulation and delayed cerebral ischemia

Cerebrovascular autoregulation differences, measured by the index of brain tissue oxygen pressure reactivity, are observed between patients who suffered from a DCI and those who did not. This intrinsic cerebral mechanism to control blood flow relatively independent of the CPP was significantly diminished in those who underwent a DCI. Similarly, Jaeger et al. demonstrated a difference in cerebrovascular autoregulation in patients with a favourable and unfavourable outcome[9]. The trend towards a higher ORx when neuroimaging techniques diagnosed an impaired CBF supports previous results by other groups. Our study also support the concept that impairment in cerebrovascular autoregulatory capacities are an essential pathophysiological factor leading to DCI.

Trends of higher ORx values were found when perfusion-CT and TCD showed signs of symptomatic vasospasm. These findings show the potential role of bedside $PbtO_2$ and ORx monitoring as a surrogate marker of cerebral autoregulation and potentially to detect DCI.

Although still controversial[27], our preliminary findings are encouraging since they support the clinical use of the bedside monitoring of $PbtO_2$ and ORx values and their validity in providing precious information concerning DCI and patient prognosis [9,10,14,15,28–31].

5.2 The relationship between cerebral blood flow autoregulation and brain metabolism

As seen in other studies[32,33] a decreased microdialysis-glucose concentration when regional $PbtO_2$ tends to reach 10mmHg or below, as seen in vasospasm, was a relevant finding. It is now believed that the aetiology of this low MD-glucose is multifactorial[34]. There is a reduction of the oxidative neuronal metabolism and an increase in anaerobic glucose metabolism. However, in some cases that showed a poor correlation with positron emission tomography (PET)-defined ischemia and low MD-glucose, this change may be associated with hyperglycolysis rather than a reduction of the oxygen and glucose supply because of reduced cerebral perfusion[35].

The LPR>40 is currently used as a threshold for brain cell hypoxia[6;7]. It has been repeatedly proven that the injured brain could use other substrate than glucose to maintain its activity,

including lactate. A significant LPR difference couldn't be assessed in the ORx subgroups. However it is now believed that other mechanisms than ischemia (i.e. increased glycolysis) [20] might explain elevated lactate and pyruvate.

5.3 Study limitations

Our CMD and $PbtO_2$ data come from a regional monitoring, and thus may not reflect the global metabolism. Our results may have been disturbed by the fact that the $PbtO_{2\ and}$ CMD measurements are easily displaced inducing long period of incorrect readings. Our patient cohort is limited in size and despite the fact that our data were collected prospectively it was analysed retrospectively. The results of this study need to be considered as preliminary but encourage future investigation and prospective studies to confirm the value of $PbtO_2$ monitoring after SAH.

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