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Continuous Assessment of Cerebral Autoregulation With Near-Infrared Spectroscopy in Adults After Subarachnoid Hemorrhage

Christian Zweifel, MD; Gianluca Castellani, MD; Marek Czosnyka, PhD; Emmanuel Carrera, MD; Kenneth M. Brady, MD; Peter J. Kirkpatrick, MD, FMedSci; John D. Pickard, FRCS, FMedSci; Peter Smielewski, PhD

Background and Purpose—In patients with subarachnoid hemorrhage, the assessment of cerebral autoregulation aids in prognosis as well as detection of vasospasm. Mx is a validated index of cerebral autoregulation based on measures of cerebral perfusion pressure and mean flow velocity on transcranial Doppler but is impractical for longer-term monitoring. Near-infrared spectroscopy is noninvasive and suitable for continuous monitoring of cerebral tissue oxygenation using the Tissue Oxygenation Index. In this study, we compared near-infrared spectroscopy-based indices of cerebral autoregulation (TOx) with Mx in patients with subarachnoid hemorrhage.

Methods—Arterial blood pressure, intracranial pressure, mean flow velocity, and Tissue Oxygenation Index were recorded. Mx and TOx were calculated as moving correlation coefficients between 10-second averaged values of cerebral perfusion pressure and mean flow velocity and between cerebral perfusion pressure and Tissue Oxygenation Index. We also calculated TOxA, the moving correlation coefficient between arterial blood pressure and Tissue Oxygenation Index.

Results—Fifty-one recording sessions were performed in 27 patients with subarachnoid hemorrhage with a total duration of 62.5 hours. Correlations of Mx and TOx over time varied markedly among individual recordings. However, time-averaging over the entire recording interval in each of the 51 recordings, we found correlations between Mx and TOx and between Mx and TOxA were highly significant. This correlation was even stronger after correction for multiple sampling for each patient, reaching $r=0.81$ for Mx and TOx and $r=0.72$ for Mx and TOxA.

Conclusion—Near-infrared spectroscopy can be used to continuously assess cerebral autoregulation in adults after subarachnoid hemorrhage. (*Stroke*. 2010;41:1963-1968.)

Key Words: cerebral autoregulation ■ near-infrared spectroscopy ■ subarachnoid hemorrhage ■ transcranial Doppler

Cerebral autoregulation (CA) is the intrinsic ability of cerebral vessels to maintain constant, steady-state cerebral blood flow (CBF) despite changes in cerebral perfusion pressure (CPP). When CA is disrupted, changes in arterial blood pressure (ABP) or intracranial pressure (ICP) aggravate cerebral edema and brain tissue hypoxia. Assessment of cerebral autoregulation and its clinical impact have been extensively reviewed.¹⁻³ Mx (from “mean velocity index”) is a crossvalidated index of CA and can be determined by calculating the correlation coefficient between spontaneous slow changes of CPP and cerebral blood flow velocity (FV) measured with transcranial Doppler (TCD).⁴⁻⁸ The importance of Mx in the acute phase of subarachnoid hemorrhage (SAH) and its clinical impact on occurrence of vasospasm and on outcome has been previously studied. In these studies, Mx has been shown to correlate with outcome in SAH and with FV in patients with SAH with cerebral vasospasm.^{9,10} Because Mx is derived from the TCD signal, its use for long-time monitoring is impractical due to loss of signal

during longer recordings caused by TCD probe displacement or decay of the ultrasound gel interface.

Near-infrared spectroscopy (NIRS) is another noninvasive technique that can provide a surrogate marker of changes in CBF in the form of a Tissue Oxygenation Index.¹¹ In contrast to TCD, the NIRS sensors are very easy to apply (the probes attach to the forehead with self-adhesive pads) and do not require frequent calibration making them more suitable for long-term monitoring. It has been shown that NIRS is able to assess CO₂ reactivity in healthy adult volunteers and the static rate of CA in pediatrics with head injury and encephalitis.^{12,13} Because the modern generation of NIRS is able to detect spontaneous, very low and low-frequency oscillations, this technique has been proposed for the continuous assessment of autoregulation.¹⁴⁻¹⁶ Brady et al demonstrated using controlled reduction of ABP in a piglet model in which autoregulation indices derived from NIRS and from cortical blood flow using laser Doppler flowmetry were significantly correlated. They were able to detect reliably the lower threshold of CA

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as defined using the flowmetry signal.¹⁷ A high coherence of slow wave fluctuations of TCD-FV and NIRS-Tissue Oxygenation Index signals in slow wave spectrum has been demonstrated in a cohort of patients with sepsis.¹⁸ This finding led to the definition of TOx, a moving correlation coefficient between slow waves in Tissue Oxygenation Index and CPP, as a possible substitute for Mx. Steiner et al found a significant correlation of Mx and TOx in their cohort of patients, although they could only use ABP instead of CPP in their calculation. However, because CA is defined as changes of CBF due to oscillations of CPP, the latter should be taken into account, especially where ICP elevation is anticipated.¹⁹

We hypothesized that NIRS might be a valuable tool to assess CA and compared the established TCD-based index Mx with the CA index TOx using the Tissue Oxygenation Index in a group of patients with SAH.

Methods

All patients included in this study were admitted to the Neurosciences Critical Care Unit at Addenbrooke's Hospital (Cambridge University Hospitals National Health Service Foundation Trust) and studied prospectively with approval of the local research ethics committee. Written informed permission was obtained from the next of kin of each patient.

Patients

Inclusion criteria were: presence of a nontraumatic SAH, age >18 years, and availability of ICP monitoring. Patients in whom a sufficient quality TCD signal from the middle cerebral artery (MCA) could not be obtained were also excluded. The patients were managed according to Addenbrooke's Neurosciences Critical Care Unit protocol.²⁰ Basic clinical data were collected and neurological status was graded according to World Federation of Neurological Societies.²¹ The amount and location of blood on CT scan were classified according to Fisher grading.²² The cause of bleeding, location, and treatment were noted. The outcome was assessed according to the modified Rankin Scale.²³

Near-Infrared Spectroscopy

The NIRO 200 monitor (Hamamatsu Photonics UK Ltd, Hertfordshire, UK) was used to monitor cerebral oxygen saturation in all the included patients. It uses a method that combines the multidistance measurements of optical attenuation. The underlying mathematical model is based on the light diffusion equation rather than Beer-Lambert law.²⁴ The NIRO 200 generates 3 wavelengths of infrared light (775, 810, and 850 nm) using 1 emitting laser diode and 2 detecting photodiodes to measure the ratio of oxygenated hemoglobin to total hemoglobin. The corresponding percentage value is expressed as the Tissue Oxygenation Index.

Signal Acquisition

ABP was measured directly from the radial or femoral artery (Baxter Healthcare Corp, CardioVascular Group, Irvine, Calif). ICP was monitored using an intraparenchymal probe (Codman ICP MicroSensor; Codman & Shurtleff Inc, Raynham, Mass) or an extraventricular drainage system with a pressure transducer (Baxter). During recording, the extraventricular drainage was closed. FV in the MCA was monitored using TCD with a 2-MHz probe (Multidop T). These signals were digitized using an A/D converter (DT9801; Data Translation, Marlboro, Mass) sampled at frequency 50 Hz. NIRS Tissue Oxygenation Index signal was measured bilaterally over the frontal area using NIRO 200 monitor and digitally transferred to the recording computer at a frequency of 2 Hz. All the data acquisition and real-time analysis were done using a laptop PC running ICM+ software.²⁵

Patient Monitoring

Most monitored patients (n=23) were sedated, and the recording took place soon after insertion of an extraventricular drainage system

because good-quality TCD recordings from awake patients were available only in a limited number of patients (n=4). Arterial blood gas analysis was performed at the time of each recording session. Signal artifacts such as arterial line flushing and repositioning of Doppler probes were removed before analysis.

Calculation of Autoregulation Indices

Input signals of ABP, ICP, FV, and Tissue Oxygenation Index were subjected to a 10-second moving average filter. Indices of autoregulation derived from TCD (Mx) and NIRS (TOx) were calculated every 10 seconds as moving correlation coefficients between filtered signals of CPP and FV and CPP and Tissue Oxygenation Index, respectively, using a moving 300-second time window. In this way, every 10 seconds, past 30 samples of mean FV, Tissue Oxygenation Index, were correlated with 30 samples of mean CPP. In addition, similar calculations were repeated but with ABP signal used instead of CPP, thus resulting in the TOxA index. Greater (positive) Mx and TOx values indicate worse autoregulation, whereas smaller values (zero or negative) indicate better autoregulation. When bilateral recording of FV and Tissue Oxygenation Index signals were available, Mx and TOx were averaged across both sides.

Statistics

Discrete variables were summarized using counts (percentage) and continuous variables using medians (interquartile range) or means (\pm SD). Resulting Mx, TOx, and TOxA variables were averaged within an individual recording sessions. To evaluate the validity of TOx and TOxA as a surrogate of CA, we first performed linear regression between Mx and TOx, respectively, between Mx and TOxA in individual recording sessions. In a second step, we averaged individual recordings of each patient and performed a linear regression again to avoid the effect of multiple sampling. Correlation analyses were performed using the Pearson method as variables were normally distributed. Receiver operating characteristics were calculated with the area under the curve as a diagnostic measure of impaired CA. According to our own series in head-injured patients, a threshold of impaired CA must lie for Mx between 0.15 and 0.25.²⁶ Mortality indicated threshold rose from 20% to 70% when the averaged cerebrovascular pressure reactivity index increased >0.3. Mx value of 0.15 is the lowest and hence most sensitive threshold of impaired CA and this value was used to dichotomize the results for the purpose of receiver operating characteristic analysis. All statistical tests were carried out at the significance level of 0.05.

Results

From June 2008 to June 2009, 27 consecutive patients were included in the study. The characteristics of the patients are presented in Table 1. Individual recordings were performed on media the second day after hemorrhage (interquartile range, 1 to 4). In 6 patients (12%), bilateral TCD recording was done and the results of both sides were averaged. Total duration of the 51 individual recordings together was 62.5 hours that is on average 73.5 minutes (\pm 20.5) per each recording epoch. Physiological data are summarized in Table 2.

Figure 1A shows an example of Mx and TOxA curves over time in a recording interval of 1 hour. The correlation between Mx and TOx over time, and that between Mx and TOxA over time, varied markedly across recordings, ranging from -0.57 to 0.91 for Mx-TOx and from -0.70 to 0.92 for Mx-TOxA. When the correlations in all of the individual measurements were averaged (n=51), the mean *r* value was 0.28 (\pm 0.38) for Mx and TOx and 0.20 (\pm 0.40) for Mx and TOxA. Apparently, TCD- and NIRS-based indices of CA are not always positively correlated in time and may even be negatively correlated.

A reliable assessment of the autoregulatory state of the cerebral vasculature requires averaging CA values obtained over a recording interval of at least 30 minutes.^{3,17} In 51 individual

Table 1. Baseline Characteristics of the SAH Cohort (n=27)

	Patients (n=27)
Age	60 [50.5; 67]
Female	21 (74.0%)
GCS on admission	8 [5.5; 12]
WFNS	4 [2; 5]
Pupil abnormality	7 (26%)
Intensive care unit length of stay	17 [10; 23]
Imaging*	
Fisher III	8 (29.6%)
Fisher IV	19 (70.4%)
Lesion†	
ICA	4 (14.8%)
ACA	6 (22.2%)
MCA	5 (18.5%)
PcomA	4 (14.8%)
Basilar tip	1 (3.7%)
AVM	3 (11.1%)
No lesion found	4 (14.8%)
Treatment‡	
Surgery	16 (59.3%)
Embolization	5 (18.5%)
Conservative	6 (22.2%)
In-hospital mortality	5 (18.5%)
mRS at 6 months§	
0	1
1	1
2	2
3	1
5	3
6	5

Values are presented as median [lower quartile; upper quartile] or counts (%).

*Fisher CT grading scale.

†Location of the aneurysm.

‡Additional treatment was insertion of an extraventricular drainage system in 25 of 27 patients.

§Available for 13 of 27 patients.

GCS indicates Glasgow Coma Scale; WFNS, World Federation of Neurological Surgeons Scale for SAH; ICA, internal carotid artery; ACA, anterior communicating artery; PcomA, posterior communicating artery; AVM, arteriovenous malformation; mRS, modified Rankin Scale.

recordings, linear regression showed a highly significant correlation between averaged Mx and TOx ($r=0.70$, $P<0.0001$; Figure 2A, left) and between averaged Mx and TOxA ($r=0.52$, $P=0.0001$; Figure 2A, right). The fact that Mx is more strongly correlated with TOx than with TOxA is not surprising, because TOx takes CPP into account. Taking an averaged Mx value >0.15 over 1 recording interval to indicate disturbed autoregulation, we found that 13 of 51 measurements met this criterion. The area under the curve of TOx to diagnose impaired CA is 0.804 (95% CI 0.70 to 0.94, $P=0.001$) and that of TOxA is 0.706 (95% CI 0.54 to 0.87, $P=0.27$; Figure 3).

To correct the effect of multiple sampling, indices were averaged of each patient and Pearson correlation calculation was done again. The correlation for Mx and TOx was 0.81 ($P<0.0001$, Figure 2B, left) and for Mx and TOxA 0.72 ($P<0.0001$, Figure 2B, right; $n=27$ patients). Averaging for

Table 2. Baseline Data of Physiological Measurements

	Recordings (n=51)
Total recording time, hours	62.5
Mean recording time per session, minutes	73.5±20.5
Mean ABP, mm Hg	97.3±14.7
Mean ICP, mm Hg	17.1±9.0
Mean CPP, mm Hg	80.1±15.8
Mean FV, cm/s	64.2±31.5
Hematocrit, %	29.6±4.6
Sodium, mmol/L	143.6±4.2
pCO ₂ , kPa	4.8±0.6
pO ₂ , kPa	13.8±3.4

Values are mean±SD.

each patient led to improvements of correlation for both TOx and TOxA. The prediction model of Mx using TOx is $Mx = -0.03 + 1.06 \times TOx$ and for TOxA, $Mx = -0.13 + 1.21 \times TOxA$. The SD of the residuals was 0.16 for TOx and 0.19 for TOxA.

Discussion

In the current study, we found good agreement between CA indices assessed continuously with TCD and NIRS in 27 patients with SAH. A similar result was demonstrated in cohort of patients with sepsis taking ABP instead of CPP for calculation.¹⁸ This good agreement of TCD- and NIRS-based CA assessment is a direct consequence of the finding that NIRS-based cerebral oximetry is able to detect intracranial slow fluctuations in its modalities,^{15,16} which are highly coherent with slow waves recorded in MCA blood flow velocity (Figure 1A).¹⁸ In the past, it has been criticized that the NIRS measurements are also affected by skin and bone oxygenation changes, but the underlying mathematical models of a new generation of monitors and in particular of NIRO 200 are able to exclude the extracranial component efficiently.^{24,27} Furthermore, the Tissue Oxygenation Index has also been shown to be independent of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer underlying the optodes.²⁸

Cerebral autoregulation plays a very important role in avoiding secondary insults due to ischemia or cerebral edema in patients with SAH.²⁹ Its assessment can be performed using interventions involving manipulation of CO₂, ABP, or simple tests like brief compression of the internal carotid artery (transient hyperemic response test).^{3,30} Alternatively, it can be assessed by examining observations of spontaneous events, like in brain tissue oxygen reactivity index³¹ or the TCD-based index, Mx.¹⁰ The intervention-based CA assessment is more precise and has a good signal-to-noise ratio but needs an experienced investigator and offers merely a snapshot of the autoregulatory state.³ Moreover, it might not be suitable or even it might be dangerous for some patients in neurocritical care. CA assessment relying solely on observation of spontaneous events does not need any intervention and can be performed continuously. However, the monitoring period has to be longer to compensate for the inherent lower signal-to-noise ratio. Continuous CA assessment using direct measurement of brain tissue oxygenation (which is an invasive modality) is unlikely to be used in patients with good-grade SAH without existing access to the brain parenchyma.

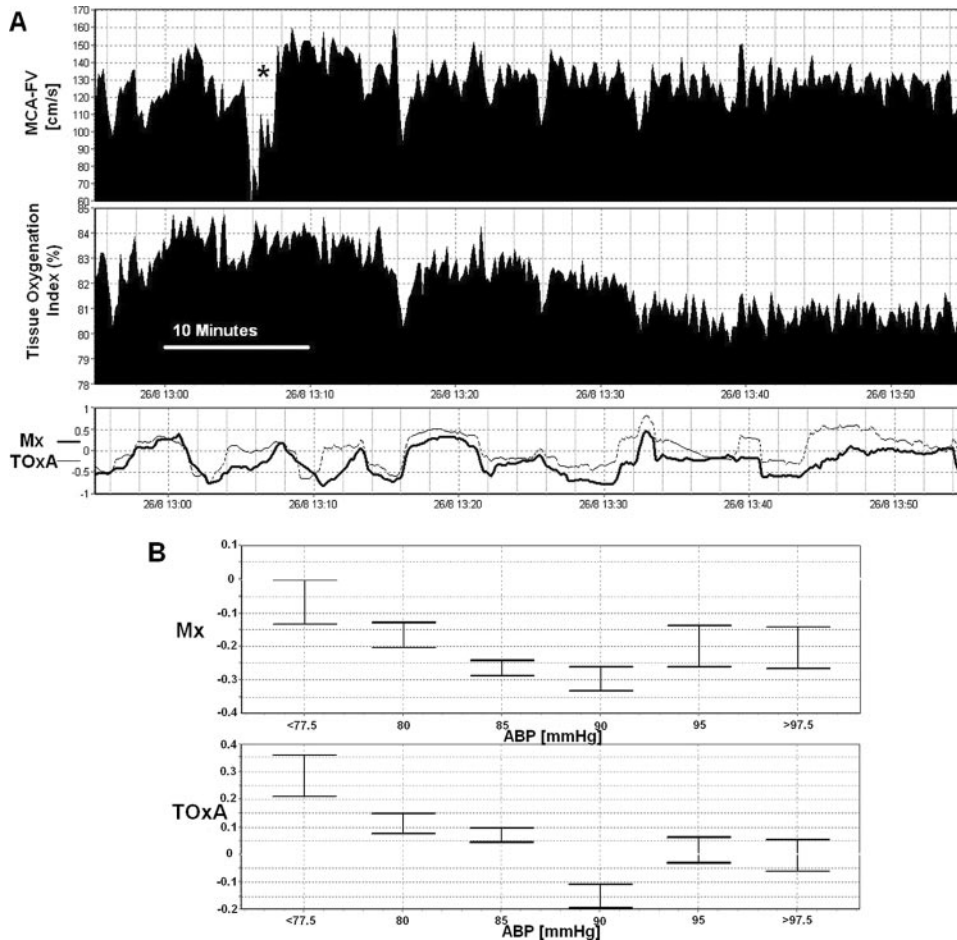


Figure 1. A, Time trends of CBF surrogates: TCD-FV and NIRS-Tissue Oxygenation Index show similar patterns in an example recording interval over 1 hour in a 40-year-old woman after SAH. Slow wave amplitudes can be seen with both modalities. TCD-derived index Mx (moving correlation coefficient of CPP and FV, thick line) and NIRS-derived index TOxA (moving correlation coefficient of ABP and TOxA, thin line) follow a similar pattern during this recording interval. *Transient loss of TCD signal. B, An “optimal” ABP may be assessed by grouping ABP values into 5-mm Hg bins and calculating averaged Mx and TOxA values, respectively, with corresponding standard deviation. A “U”-shaped curve with a minimum of Mx and TOxA at 90 mm Hg can be displayed and this is considered the “optimal” ABP, that is, ABP at which the autoregulation index reaches the lowest value and hence the best autoregulatory state.

TCD is noninvasive, but the continuous use of TCD recording is limited. On the contrary, NIRS is very robust, noninvasive, requires minimal caregiver attention, and is also suitable for patients who are alert or agitated. Required continuous ABP

measurement for calculation of TOx and TOxA is a standard monitoring technique in critical care and is minimally invasive. In other clinical scenarios, it can be replaced by noninvasive ABP monitoring systems like the Finapres finger plethysmograph.

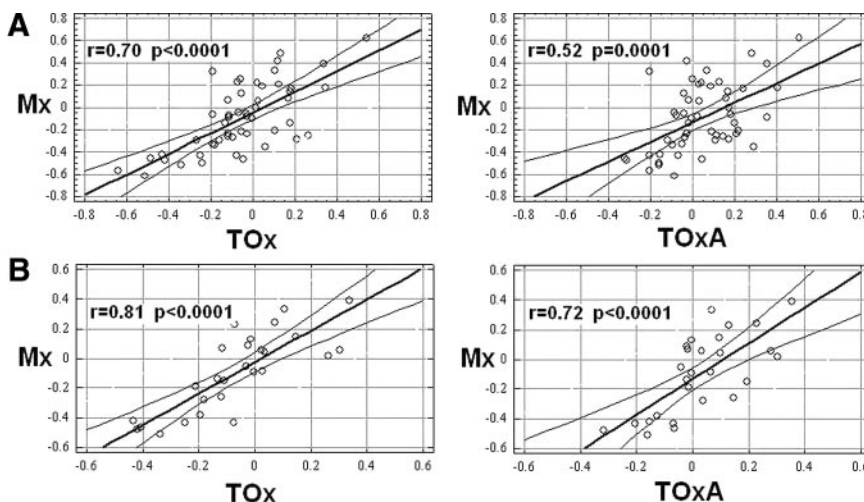


Figure 2. Linear regression plots comparing Mx and TOx and Mx and TOxA, respectively. Positive values indicate impaired CA, whereas negative values indicate intact CA. A, Pearson regression analysis of Mx and TOx in 51 recordings showed a highly significant correlation ($r=0.70$, $P<0.0001$). Also, the correlation of Mx and TOxA was highly significant in individual recordings ($r=0.52$, $P=0.0001$). B, To avoid the effect of multiple sampling, we averaged individual recordings of each patient. Pearson correlation coefficient for Mx and TOx is 0.81 ($P<0.0001$). For Mx and TOxA, the correlation is 0.72 ($P<0.0001$).

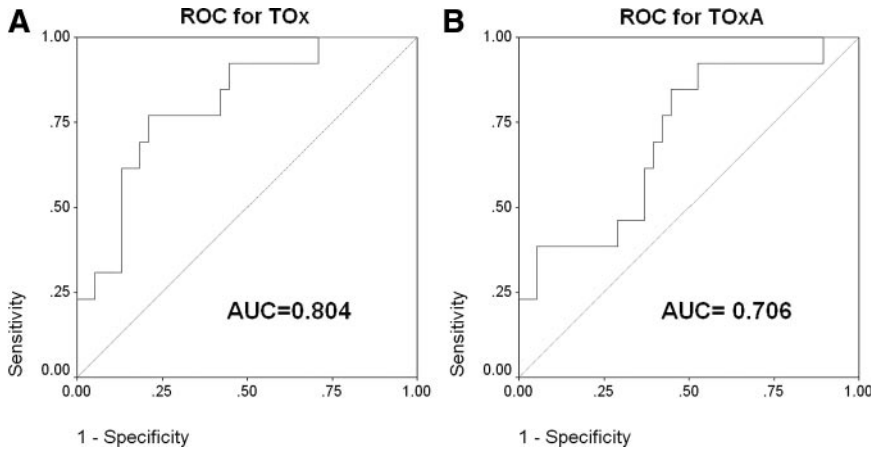


Figure 3. Receiver operator characteristics (ROCs) for TOx (A) and TOxA (B) to diagnose impaired cerebral autoregulation in 51 measurements. CA was considered impaired when Mx was >0.15 . AUC indicates area under the curve.

Continuous autoregulation monitoring may allow determination of the “optimal” ABP and CPP in patients with SAH. How this might be achieved is illustrated in Figure 1B. Data from a previous study in head-injured patients suggest that CPP optimization may be beneficial, because patients treated closer to the “optimal” CPP had a better outcome than patients treated further away.³² This is a promising concept, which may anticipate that in SAH, similar to traumatic brain injury, hypo- and hyperperfusion are both detrimental. In patients with SAH with vasospasm, however, the goal of blood pressure management is to improve oxygen delivery to ischemic tissue. This can only be effective if raising blood pressure improves CBF, that is, if the arterial pressure is set above the upper limit of autoregulation. A positive correlation between CPP and CBF indicates impaired CA and in this particular clinical scenario, it would suggest a CPP level that might be suitable for the successful treatment of ischemia.³³ Although we have demonstrated in an example (Figure 1B) that an “optimal” ABP and CPP can be traced with NIRS-derived indices in patients after SAH, targeting pressures above the “optimal” ABP may be more appropriate for patients with vasospasm. Continuous determination of CA, therefore, might still be advantageous for guidance of hypertensive therapy above the upper limit of CA. This subject requires further prospective studies.

Limitations

Despite a highly significant correlation, there are some clear discrepancies between TCD- and NIRS-assessed autoregulation values. This was particularly manifested within individual recordings, in which a correlation between TCD and NIRS indices spanned a wide range from far positive to even negative values. One important factor that is responsible for those differences is that TCD and NIRS provide 2 different types of surrogate measures of CBF. The NIRS Tissue Oxygenation Index is dependent on O_2 saturation and O_2 extraction fraction and may fluctuate with mental activation in alert patients.³⁴ Another, potentially significant issue is that the measurements are limited to specific brain regions and these regions may differ for both modalities. With TCD, only the CBF of the brain supplied by the blood flow of MCA alone is monitored, and this is in addition under the assumption of constant diameter of the MCA. The NIRS Tissue Oxygenation Index, on the other hand, reflects changes in cerebral

blood oxygenation in part of the frontal lobe and will likely include partially MCA and partially anterior cerebral artery territories. Imaging studies in head-injured patients³⁵ as well as in patients with SAH³⁶ demonstrated that cerebral autoregulation may be only selectively impaired across different brain regions. Therefore, it is possible that at times differences between Mx and TOx genuinely reflect differences in the CA. This is not necessarily a limitation of NIRS, because monitoring of CA even from a very focal brain region using direct brain tissue oxygenation measurement has been shown to be of prognostic value in patients with SAH.³¹

We could not demonstrate any significant association of cerebral vasospasm, delayed ischemic neurological deficits, or outcome with cerebral dysautoregulation in our material because it has been shown in other studies.^{10,30,37} Our recording sessions were carried out early after admission before the patients reached the phase of vasospasm. This was not by design, but rather dictated by some practical issues: presence of ICP monitoring, ability of patients to tolerate prolonged TCD measurement, and availability of the equipment. Much longer recording intervals with NIRS, stretching over several days, would be needed to warrant the assessment of NIRS-derived indices’ diagnostic value for detection of vasospasm and prediction of delayed ischemic neurological deficits.

In this article, we have only validated TOx and TOxA against Mx. This is far from ideal, but the present study did not allow any manipulation of ABP or $Paco_2$ to test, for example, the “static rate of autoregulation” and therefore no other, more precise measure of CA could be used for comparison. There is no doubt that more studies need to be done to confirm validity of NIRS-derived CA indices in different scenarios. Nevertheless, Mx has been extensively crossvalidated against other CA determination methodologies^{4–8} and the fact that TOx and TOxA correlate well with Mx is very promising.

Summary

Our results show that cerebral autoregulation can be monitored continuously easily with NIRS in patients with SAH. It can potentially be done completely noninvasively using ABP rather than CPP and thus may facilitate management of ABP in patients in whom invasive ICP monitoring is not feasible or contraindicated.

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Disclosures

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