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ORIGINAL ARTICLE

Near-Infrared Spectroscopy can Monitor Dynamic Cerebral Autoregulation in Adults

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Abstract
Objective To study the correlation between a dynamic index of cerebral autoregulation assessed with blood flow velocity (FV) using transcranial Doppler, and a tissue oxygenation index (TOI) recorded with near-infrared spectroscopy (NIRS).
Methods Twenty-three patients with sepsis, severe sepsis, or septic shock were monitored daily on up to four consecutive days. FV, TOI, and mean arterial blood pressure (ABP) were recorded for 60 min every day. An index of autoregulation (Mx) was calculated as the moving correlation coefficient between 10-s averaged values of FV and ABP over moving 5 min time-windows. The index Tox was evaluated as the correlation coefficient between TOI and ABP in the same way. The indices Mx and Tox, ABP and arterial partial pressure of CO_2 were averaged for each patient.
Results Synchronized slow waves, presenting with periods from 20 s to 2 min, were seen in the TOI and FV of most patients, with a reasonable coherence between the signals in this bandwidth (coherence >0.5). The indices, Mx and Tox, demonstrated good correlation with each other ($R = 0.81$; $P < 0.0001$) in the whole group of patients. Both indices showed a significant ($P < 0.05$) tendency to indicate weaker autoregulation in the state of vasodilatation associated with greater values of arterial partial pressure of CO_2 or lower values of ABP.
Conclusion NIRS shows promise for the continuous assessment of cerebral autoregulation in adults.

Keywords Cerebrovascular circulation · Near-infrared spectroscopy · Transcranial Doppler ultrasonography · Human · Adult

Abbreviations

ABP	Mean arterial blood pressure
CBF	Cerebral blood flow
FV	Mean blood flow velocity
Mx	Mean flow velocity index of dynamic autoregulation
NIRS	Near-infrared spectroscopy
$PaCO_2$	Arterial blood partial pressure of carbon dioxide
TCD	Transcranial Doppler
TOI	Tissue oxygenation index
Tox	Tissue oxygenation index of dynamic autoregulation

Cerebral near-infrared spectroscopy (NIRS) is an evolving technology [1]. The rationale of using NIRS to monitor cerebral autoregulation is based on the assumption that the brain's oxygen content is positively related to arterial oxygen saturation, cerebral blood flow (CBF), and oxygen-tissue diffusivity, and negatively associated with the cerebral metabolic rate for oxygen. Comparisons of changes in tissue oxygenation over short periods of time (3–6 min), taking place in response to changes in arterial pressure, with presumed stable arterial saturation, stable metabolism,

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and probably stable diffusivity, should give similar information as a comparison of changes in CBF and arterial pressure. The advantage of such a setup for clinical monitoring is potentially immense: NIRS is non-invasive, does not require frequent calibration, is fairly robust, and contrary to transcranial Doppler (TCD), the problem of a constant and precise location of the probes is not an issue. However, the use of NIRS to monitor cerebral autoregulation in adults is still debatable. In contrast to neonates, thick skulls and large head circumferences do not allow for full trans-cerebral measurements. Instead a hemispheric approach is used resulting in a sample volume that is not defined.

Newer apparatus, such as the INVOS^{TM} cerebral oxymeter (Somanetics Corporation, Troy, Michigan, USA) or the NIRO 300 or 200 (Hamamatsu Photonics, Hamamatsu City, Japan) are supposed to attenuate the influence of the extracranial circulation. This is achieved by resolving spatial differences between three emitting and detecting diodes separated by different distances. The proportion of oxygenated and deoxygenated hemoglobin is calculated not from one pair of absolute values but from the regression line between values from the three detectors. In this way, a tissue oxygenation index is calculated, which is supposed to replicate brain oxygen saturation [2]. Using the NIRO 300 in the controlled environment of carotid endarterectomy, it has been demonstrated that the tissue oxygenation index (TOI) is sensitive to changes in hemispheric, intracerebral blood supply and is little affected by extracranial contamination [3]. The TOI has also been shown to be independent of hemoglobin concentration, skull thickness, and the area of the cerebrospinal fluid layer underlying the optodes [4].

The use of NIRS to evaluate cerebrovascular reactivity to changes in $PaCO_2$ in adults was discussed in 1995 [5]. More recently, it was shown that in adults stable 0.1 Hz oscillations of hemodynamic parameters induced by regular breathing at a rate of 6/min, bring about cortical hemodynamic responses that follow specific phase relationships due to cerebral autoregulatory action and circulatory transit times which can be measured by NIRS [6]. With hemodynamic impairment, as in unilateral carotid obstruction, these phases were significantly changed reflecting disturbed autoregulation. The correlation between changes in cerebral perfusion pressure and a cerebral tissue oxygenation index over time was demonstrated to correlate with cerebral autoregulation assessed using laser Doppler cortical blood flow during experimental intracranial hypotension in piglets [7]. A similar technique proved to be promising in neonates [8].

Cerebral autoregulation is increasingly being recognized as a potentially interesting monitoring parameter in neurocritical care. Disturbed autoregulation has been shown to be associated with unfavorable outcome after head injury [9], vasospasm after subarachnoid hemorrhage [10], and the possibility to use autoregulation to define an individual target for cerebral perfusion pressure is suggested (recommendation, level III) in the latest edition of the Brain Trauma Foundation Guidelines for the management of severe traumatic brain injury [11].

We compared a validated TCD index of autoregulation (Mx) [9] with a measure of autoregulation utilizing the TOI in a group of patients suffering from sepsis, severe sepsis, or septic shock.

Methods

Data were prospectively collected during a clinical study focusing on septic encephalopathy in the medical and surgical intensive care units of the University Hospital of Basel, Switzerland (www.clinicaltrials.gov Identifier NCT00410111). The protocol was approved by the Regional Ethical Committee and written consent was obtained from all patients or their next of kin. The main aim of the clinical study was to investigate various indices of cerebral perfusion and metabolism as markers of delirium in sepsis [12].

As a part of the measurement protocol we studied the relationship between Mx [9] and dynamic changes of cerebral tissue oxygenation measured using the TOI provided by a NIRO 200 monitor (Hamamatsu Photonics, Solothurn, Switzerland). Inclusion criteria were age >18 years and sepsis, severe sepsis, or septic shock without an intracranial focus of infection. Patients with a history of cerebrovascular or intracranial neurological disease were excluded.

Mean arterial blood pressure (ABP) was measured directly from the radial or femoral artery. Patients were monitored for 1 h every day on up to four consecutive days, depending on their length of stay in the intensive care unit or survival. NIRS measurements were performed bilaterally over the frontal to frontoparietal area. Blood flow velocity (FV) in the middle cerebral artery of both hemispheres was monitored concurrently using TCD with a 2-MHz probe (Multidop T, DWL, Germany). Analogue outputs from direct arterial pressure monitoring, and TCD and digital NIRS data (1 Hz) from the serial output of the NIRO 200 were transferred to a laptop computer via an analogue-to-digital converter where necessary and were processed using the "ICM^{+} software", version 6.1, from the University of Cambridge, UK [13].

Information regarding cerebral autoregulation is included in so-called slow (20 s–3 min) vasocycling of cerebral blood flow [9]. In a first step the coherence function between FV and TOI signals was analyzed. Absolute values of the coherence function (see Fig. 1) indicate the distribution of the 'correlation coefficients' of the

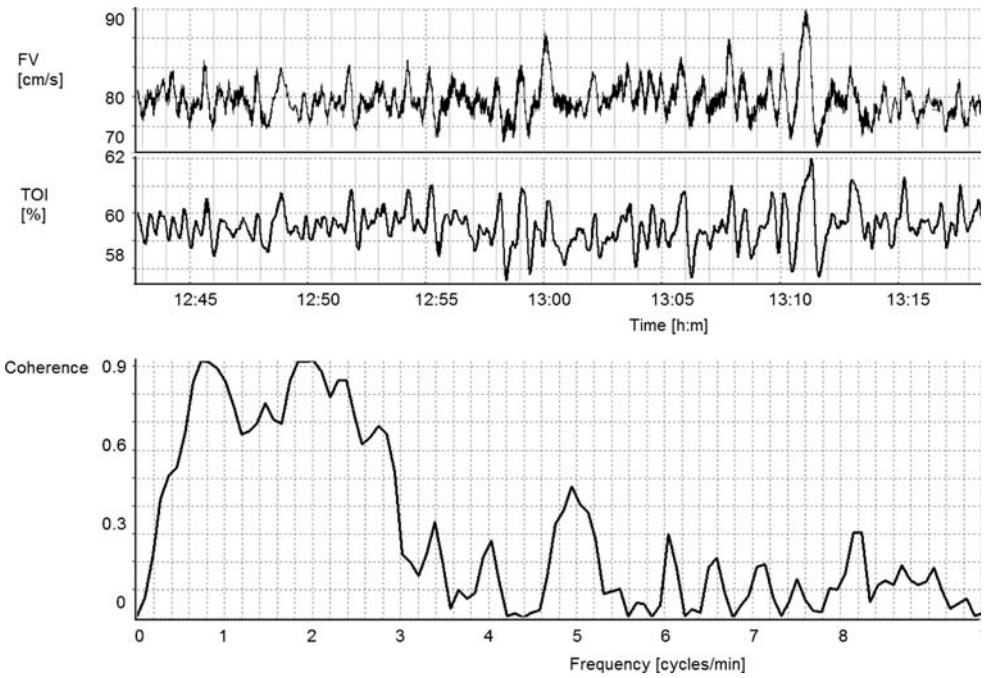

Fig. 1 Slow waves of flow velocity (FV) measured with transcranial Doppler and of a tissue oxygenation index (TOI) measured with near-infrared spectroscopy (NIRS). Both signals were moving-averaged with a time window of 10 s. The bottom graph shows a high coherence between waves in the 0.5–3 cycles/min frequency band equivalent to periods of 20 s–2 min. High coherence indicates that slow waves detected by TCD and NIRS in this frequency band are similar; therefore, NIRS may have a potential use for dynamic autoregulation assessment similar to the well-established use of TCD

components of both signals in different frequency ranges. High values (close to +1) indicate that both signals contain components of high correlation. If changes in FV (proportional to changes in CBF) are useful for the assessment of cerebral autoregulation, and high values for coherence are found, similar information is included in TOI.

Cerebrovascular autoregulation was assessed by calculating Mx as a correlation coefficient between 30 10 s averages of ABP and FV signals [9, 14]. Accordingly, Mx was calculated from a 5 min time-window, and this window was moved every 60 s. A positive Mx value indicates impaired autoregulation, and a zero or negative correlation coefficient intact autoregulation (see Fig. 2). The Mx index has previously been validated by comparison to the static rate of autoregulation [15], the transient hyperemic response test [16], the leg-cuff test of cerebral autoregulation [14], the autoregulation index ARI [17], the pressure-reactivity index PRx [18], the phase shift between slow waves of FV and ABP [19], and the CO_2 reactivity test [20]. Using the same principle, a moving correlation coefficient between 10 s averages of ABP and TOI signals (Tox) was calculated. A similar index, using the INVOS^{TM} cerebral oxymeter, was validated in piglets using laser Doppler flowmetry and cerebral perfusion pressure measurements during graded hypotension experiments [7]. Values from the right and left hemisphere from TCD and NIRS were averaged for analysis. In this group of patients, without a history of cerebrovascular disease, this will not introduce a bias.

Time-averaged values from every examination (average period of monitoring of 60 min) were used for analysis. Analysis of variability of autoregulation indices was performed using individual examinations ($n = 81$). Comparisons between Mx, Tox, ABP, and arterial partial pressure of CO_2 ($PaCO_2$) were performed between averaged values of all daily measurements performed in each patient ($n = 23$). SPSS 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data.

Results

Mean patient age (SD) was 68 [18], 39% were women. Mean APACHE II Score was 22 [7]. Thirteen patients suffered from pneumonia, eight from intra-abdominal infections, and one patient each from soft tissue and joint infection. Fifteen patients needed norepinephrine for stabilization of arterial blood pressure, six patients received dobutamine in addition to norepinephrine. No patient received antihypertensive drugs.

For each raw data file (representing 60 min of recording; $n = 81$) time trends of 10 s averages of TOI and FV both revealed the presence of variable intensity slow waves with periods ranging from 20 s to 2 min. Coherence analysis indicated a good level of association between the two trends (value >0.5) in a frequency band from 0.5 to 3 cycles/min (Fig. 1). This finding suggests that both FV and TOI signals contain similar slow waves, potentially carrying information on cerebral autoregulation.

Individual recordings revealed the same slow wave character for the relationship between FV and ABP (Mx), and between TOI and ABP (Tox) in cases of defective

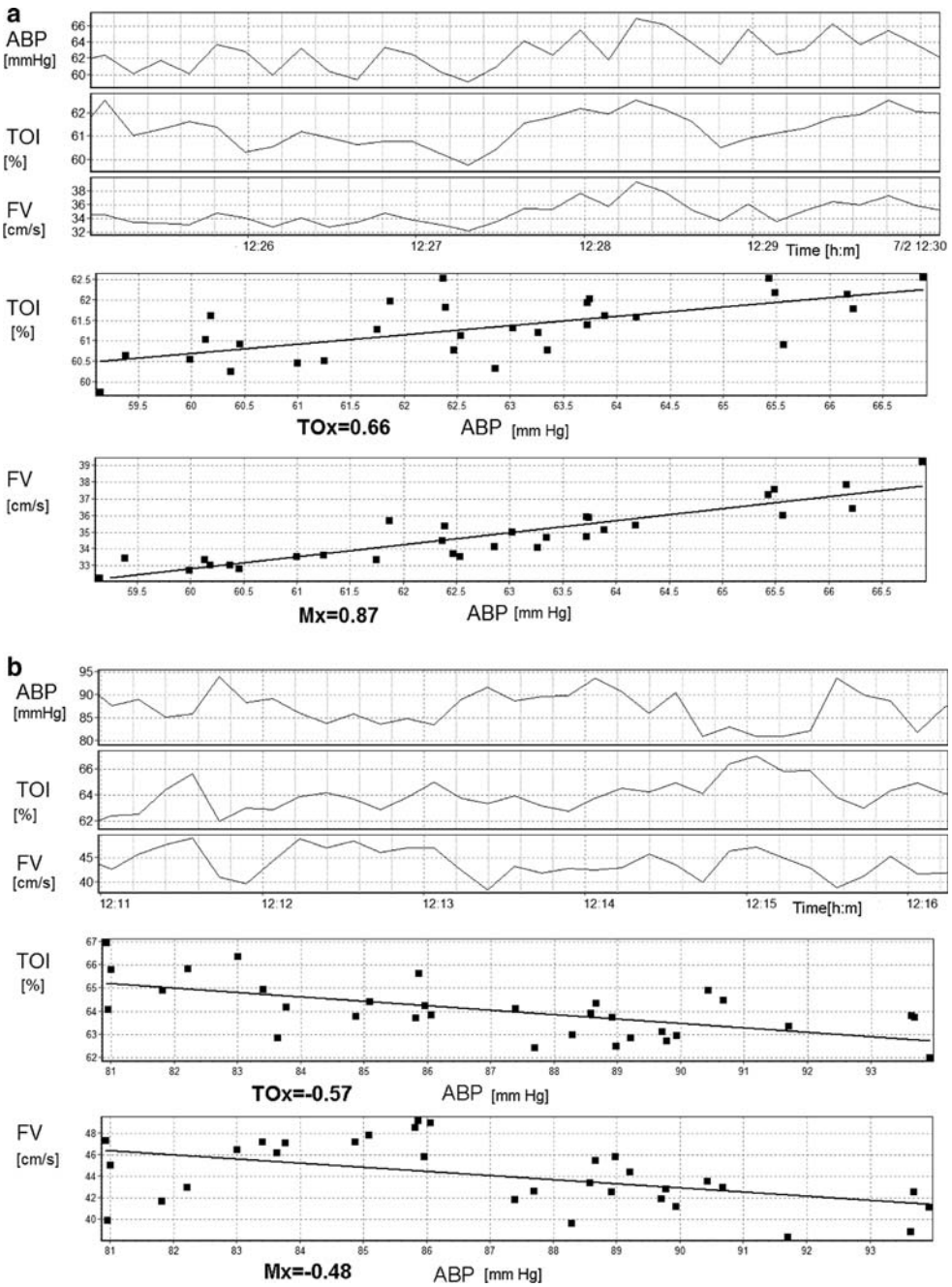

Fig. 2 (**a**) Example of passive transmission between slow waves of mean arterial blood pressure (ABP), a tissue oxygenation index (TOI) measured with near-infrared spectroscopy, and flow velocity (FV) measured with transcranial Doppler with a positive value of the index of autoregulation Tox (upper panel). The same regression between ABP and Mx produces a positive index Mx (lower panel). This pattern is specific for disturbed autoregulation. (**b**) Example of active regulation of CBF which produces a negative correlation between ABP and TOI (Tox is negative, upper panel). The correlation between ABP and FV is also negative (lower panel)

(Fig. 2a), and functional (Fig. 2b) autoregulation. Overall, the regression between Tox and Mx in this group of 23 patients showed a strong positive association between the two indices ($R = 0.81$; $P < 0.0001$, Fig. 3). The regression model for the prediction of Mx using Tox is as follows: Mx = 0.14 + 1.53 Tox. The bias for the model (mean value of residuals) was 0.0002 with a standard deviation of 0.17. The 95% confidence limits for the prediction of Mx using Tox were ±0.34.

Both indices were related to the $PaCO_2$ (Mx: $R = 0.43$; $P < 0.03$ and Tox: $R = 0.49$; $P < 0.02$; $n = 23$), indicating that $PaCO_2$-induced dilatation of flow-regulating vessels was associated with worse autoregulation.

Similarly, there was a strong correlation between Mx and ABP ($R = -0.65$; $P < 0.001$; $n = 23$) and between Tox and ABP ($R = -0.57$; $P < 0.005$; $n = 23$). These relationships indicate that at lower arterial pressures disturbance of autoregulation is more likely to happen, due to a potentially shorter distance to the lower limit of autoregulation.

Day-to-day variations of autoregulation are likely to exist and may reflect changes in the clinical status, $PaCO_2$,

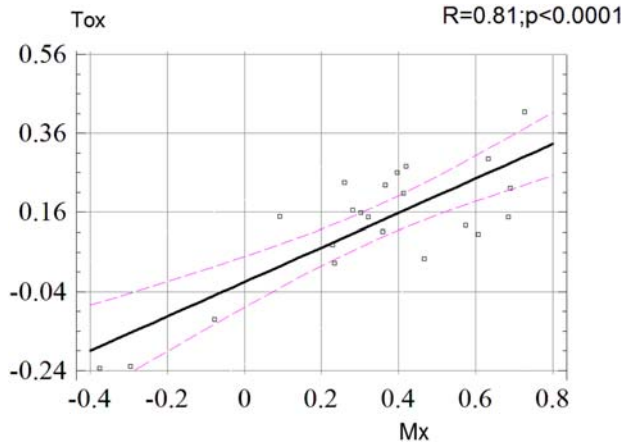

Fig. 3 Regression between averaged values of Tox and Mx in 23 patients suffering from sepsis, severe sepsis, or septic shock indicates a good correlation between these two modalities

ABP, etc.—see example in Fig. 4. The average standard deviation of Tox within patients was 0.17 as compared to standard deviation between patients of 0.11. The range of within-patient variations was 0.029–0.27.

Discussion

Slow, synchronized waves of periods from 20 s to 2 min, as seen in FV, and traditionally used for the assessment of cerebral dynamic autoregulation using various models [9, 21–23], can also be observed in NIRS-derived TOI. Interestingly, such slow waves are usually not observed in directly measured brain tissue oxygenation. This may be due to the fact that NIRS-derived TOI mainly reflects oxygenation in cerebral venous blood, whereas direct methods reflect oxygenation in brain tissue. Diffusivity of oxygen from blood to tissue may delay the fast fluctuations of TOI, evidently related to vasomotion-induced acceleration and deceleration of CBF. Similarly, changes in TOI related to fluctuations in brain metabolism are probably much slower and, without stimulation, may rarely happen in repetitive fashion, particularly in sedated patients. Therefore, Tox may be much more precise in the assessment of autoregulation, than an index of oxygen reactivity derived from changes in direct brain tissue oxygen content and cerebral perfusion pressure [24].

The phenomenon of fluctuations of TOI, synchronous with slow waves in FV, may open new perspectives for the continuous non-invasive monitoring of cerebral autoregulation using NIRS. Such a possibility was explored previously [6, 25–27], but in the present study, the methodology was used consistently for the first time in a clinical trial in adults. We demonstrate a surprisingly good correlation between the established Mx index of autoregulation [9, 15, 20] and this new NIRS-based index, Tox. Both indices react to $PaCO_2$-induced vasodilatation, demonstrating a worsening of cerebral autoregulation. Also, both seem to react to arterial hypotension, indicating a gradual decrease of autoregulatory reserve. However, unlike TCD probes, the optodes of modern NIRS devices can be fixed on the forehead of patients using double-sided stickers, thus avoiding the problem of probe dislocation which seriously limits the quality of long-term TCD recordings. Furthermore, loss of signal during longer recordings due to drying of the jelly used with TCD is also not an issue. Finally, potential small displacements of the optodes over longer periods will not disturb the quality of monitored

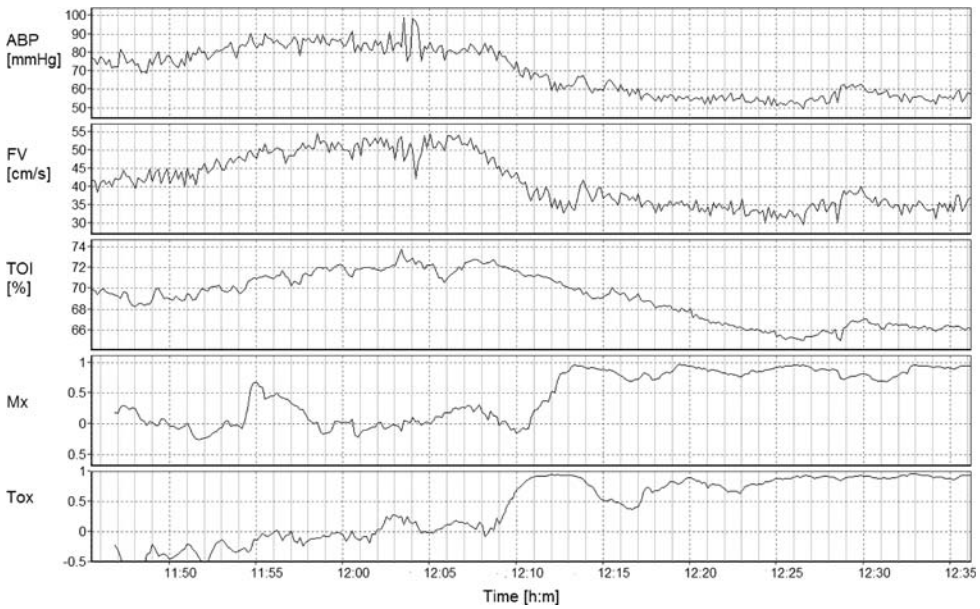

Fig. 4 Example of rapid worsening of cerebral autoregulation in response to spontaneous arterial hypotension. Flow velocity (FV) and the tissue oxygenation index (TOI) decrease around 12:05, and the indices Tox and Mx both increase toward values close to +1

variables as heavily as movement of TCD probes. On the other hand, NIRS measurements are susceptible to ambient light and shielding of the optodes is necessary.

Tox is, as Mx, a dimensionless index, which makes it ideal for comparisons between patients. Positive values around +1 indicate disturbed autoregulation, and values around zero and negative values good autoregulation. Negative values of Mx are interpreted as a reflection of the negative slope of the CBF-ABP curve, often seen just above the lower limit of autoregulation, particularly with hypocapnia. This is, most probably, also the case with the index Tox. The index Mx is used as a continuous descriptor of autoregulatory reserve. Using any threshold values for Mx is difficult due to the fact that autoregulation derived from FV in the middle cerebral artery is not necessarily representative for the whole brain, and in pathology, autoregulation may be patchy even within the territory of the middle cerebral artery. For clinical convenience, in head injured patients Mx greater than 0.5 indicates definitely disturbed autoregulation which translates to a value above 0.3 for the index assessed using cerebral perfusion pressure rather than arterial pressure alone [28]. From the regression formula, critical values for Tox should be set between 0.2 and 0.3. Obviously, like Mx and other methods used for continuous analysis of autoregulation, Tox should be verified for different pathologies and in healthy volunteers. If verified, it could become a powerful tool to facilitate brain monitoring in clinical neurosciences.

Limitations

Possible limitations of the study are the small number of patients, the selected patient population, the indirect evaluation of Tox based on Mx rather than on a direct evaluation using, e.g. CO_2 reactivity or a standardized blood pressure change. In this observational study blood pressure was not challenged. Spontaneous changes of ABP (slow fluctuations of periods from 2 min to 20 s) were used instead. Similarly, spontaneous differences in $PaCO_2$, resulting from different respiratory regimes were used for analysis. $PaCO_2$ was monitored using arterial blood gas analysis. We did not include a control group of healthy volunteers to compare Tox and Mx. A correlation between a new index of autoregulation (Tox) and Mx, an established index of autoregulation [9, 15, 19–22] requires comparisons of the variables across a group of patients with both good and disturbed autoregulation. Patients with sepsis are ideal for this purpose, as they have a large spectrum of autoregulatory depletion. Moreover, a comparison of volunteers to medicated, ventilated patients may be misleading. This has been partially discussed previously [29]. Both Tox and Mx show rapid variations which may be caused by changes in the intensity of useful components for the assessment of autoregulation (slow waves) or fast changes in the strength of dynamic regulation (see example in Fig. 4). A reasonable time of averaging (minimum of 30 min) is necessary to achieve reliable results.

Conclusion

Vasocycling, i.e. waves of periods from 20 s to 2 min seen in cerebral blood flow velocity can be also recorded in the NIRS-derived tissue oxygenation index, TOI. Indices of dynamic autoregulation assessed using NIRS and TCD are in agreement in adults with sepsis.

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Competing Interests The ICM+ software (www.neurosurg.cam.ac.uk/icmplus) used for data recording and analysis is licensed by Cambridge Enterprise Ltd, Cambridge, UK. PS and MC have an interest in a part of the licensing fee.

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