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ORIGINAL ARTICLE

Critical Thresholds for Transcranial Doppler Indices of Cerebral Autoregulation in Traumatic Brain Injury

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Abstract
Background Transcranial Doppler-derived indices of cerebral autoregulation are related to outcome after TBI. We analyzed our retrospective material to identify thresholds discriminative of outcome for these indices.
Methods 248 sedated and ventilated patients after head injury were eligible for the study. The indices of autoregulation derived from transcranial Doppler were calculated as correlation coefficients of blood flow velocity with cerebral perfusion pressure (index Mx) or arterial blood pressure (index Mxa). 2 × 2 tables were created grouping patients according to survival–death or favorable–unfavorable outcomes and varying thresholds for Mx and Mxa. Pearson's chi-square was calculated. Thresholds returning the highest chi-square value were assumed to have the best discriminative value between survival–death and favorable–unfavorable outcomes.
Results Mx and Mxa demonstrated that worse autoregulation is associated with poorer outcome and greater mortality ($P = 0.0033$ for Mx and $P = 0.047$ for Mxa). Both indices were more effective for prediction of favorable outcome than mortality. Chi-square for Mx showed a double peak with thresholds at 0.05 and 0.3. Mxa had only one peak at 0.3. Peak chi-square for Mx (11.3) was greater than for Mxa (8.7), indicating that Mx was a better discriminant of outcome than Mxa.
Conclusions We propose that Mx greater than 0.3 indicates definitely disturbed autoregulation and lower than 0.05 good autoregulation. For values between 0.05 and 0.3 the state of autoregulation is uncertain.

Keywords Head injury · Transcranial Doppler · Outcome · Thresholds · Autoregulation index

Introduction

The importance of the measurement of cerebral autoregulation has been highlighted in many studies over the past decades [1–3]. Continuous monitoring seems to be important as autoregulation status may change dynamically—e.g., during plateau waves of intracranial pressure (ICP) [4], incidental arterial hypotension [5], vasospasm, hyperemia [6], or refractory intracranial hypertension [7].

The mean flow velocity index (Mx) is a correlation coefficient between slow fluctuations (whose average period ranges from 20 s to 3 min) of flow velocity (FV) in the middle cerebral artery (MCA), measured through TCD, and global cerebral perfusion pressure (CPP). It has been postulated that when there is a direct relationship between these two factors (index is positive), the cerebrovascular autoregulation is impaired [8]. Zero or negative index signifies intact autoregulation. Mxa is a similar index, derived from the correlation between FV and mean arterial

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blood pressure (ABP), and is correlated with Mx [9]. This index can substitute Mx in cases when ICP is not monitored for clinical choice or technical reasons.

The Mx/Mxa methodology has been cross-validated against gold-standard methods—static rate of autoregulation [10], leg-cuff test, and transient hyperemic response test [11]. Mx has been shown to correlate with outcome in a variety of pathological conditions, including severe head injury [12], subarachnoid hemorrhage [13], and stroke [14].

Even though a threshold of 0.3 for Mx has been intuitively used in previous studies to differentiate between patients with impaired and intact autoregulation [12], the clinical significance of this value has never been validated in a larger sample of patients. Therefore, we conducted a retrospective study by analyzing the data from our database of head injured patients, with the aim of identifying a critical threshold for survival and favorable outcome in TBI patients.

Methods

Patients

Our database included 763 patients admitted for traumatic brain injury to the Neurosciences Critical Care Unit (NCCU) of Addenbrooke's Hospital, Cambridge, from 1992 to 2009. For this study, the inclusion criteria were: availability of ICP, CPP, daily TCD recordings for assessment of Mx and Mxa indices, known age, Glasgow Coma Scale score on admission and 5-point Glasgow Outcome Scale at 6 months. As a result, a total of 248 patients were available for analysis.

Before 2000, a classic CPP-oriented protocol was used for the management of patients [15]. Later, a combined CPP/ICP protocol was introduced with subsequent modifications. All patients were intubated and mechanically ventilated to achieve SpO_2 of at least 93% and $PaCO_2$ between 4 and 4.5 kPa. Continuous infusion of propofol or midazolam was used for sedation, fentanyl for analgesia, and atracurium for paralysis when clinically required. The target CPP was 70 mmHg, but a CPP of 60 was accepted provided that ICP was not higher than 20 mmHg. A sustained increase in ICP above 20 mmHg was actively treated according to our in-house protocol [16].

Monitoring and Data Analysis

ICP was monitored continuously using micro-transducers (Camino Direct Pressure Monitor, Camino Laboratories, San Diego, CA; or Codman Micro Sensor, Johnson & Johnson Professional, Rynham, MA), inserted intraparenchymally into the frontal region. Arterial blood pressure was monitored directly from the radial or dorsalis pedis artery (System 8000, S & W Vickers Ltd, Sidcup, UK or Solar 6000 System, Marquette, USA). The MCA on the side of the ICP measurement was insonated daily at a depth of 40–60 mm for a period of 20 min to 2 h starting from the day of admission until day 3 after head injury, using the PCDop 842 Doppler Ultrasound Unit (Scimed, Bristol, UK) or Neuroguard (Medasonics, Fremona, CA). Signals were monitored during periods of stability, away from physiotherapy, tracheal suction, and other disturbances. Monitoring of ICP and ABP supported by computer software (WREC and later ICM+ [17], Cambridge Enterprise) was an accepted method aiding the clinical management of patients. The recorded data were analyzed anonymously as part of a clinical audit. Before 2003, no individual consent from a next of kin was required—the method for monitoring and analysis was accepted by the Neuro Critical Care Users Committee and included as a standard clinical assessment of cerebral autoregulation. Later, only patients individually consented under approval of the Local Ethics Committee, participating in various NCCU and Wolfson Brain Imaging Center (University of Cambridge, UK) research protocols, were included.

Raw signals of ICP, ABP, and FV were sampled with a frequency of 30–70 Hz. From these signals, 10-s averages were calculated: mABP, mFV, mICP. Mean cerebral perfusion pressure (mCPP) was calculated as mABP − mICP. 30 consecutive samples from a moving window with a width of 5 min were taken to calculate Pearson's correlation coefficients between mFV and mCPP (Mx) or mFV and mABP (Mxa). The window was then moved by a set number of "M" samples. The last "M" samples from the buffer for correlation were removed and "M" samples were added to the front of the buffer (in the calculations used here, $M = 1$, i.e., the buffer was moved by 10-s intervals) and new values of Mx and Mxa were calculated. In this way, the indices Mx and Mxa formed time series in parallel to other signals. Mx, Mxa, and other variables (ABP, ICP, CPP, FV) were averaged for the whole recording period (recording lasted from 10 min to 3 h), and then again for recordings performed on consecutive days for the same patient. The result was a mean value describing the overall autoregulatory status of a patient during the whole period of monitoring (ranging from 1 day to 15 days after injury). These values were used for comparison with outcome after injury and other clinical parameters.

Statistical Analysis

All statistical analyses were performed using the SPSS software package (IBM Inc.). A series of 2 × 2 tables was created grouping patients according to the following criteria (1) survival or dichotomized outcome (GOS 1–3 vs.

4–5) and (2) Mx and Mxa values above or below sequential thresholds (in 0.05 steps). Pearson's chi-square was calculated for each of these tables. For each outcome measure, the respective threshold returning the highest chi-square score was assumed to have the best discriminative value. The used method of sequential chi-squares has been preferred over ROC curves in the phase of statistical design of the study, because it proved to be able to provide more reliable results with sharper thresholds.

Results

The median age of the patients was 28 years (range 3–78, IQR 22) and the median admission GCS was 6 (range 3–15, IQR 4). 195 of the patients were males (79%). Six months after admission, 51 patients had died (20.6%), 8 were in a vegetative state (3.2%), 61 were severely disabled (24.6%), 56 were moderately disabled (22.6%), and 72 had recovered completely (29%).

The distributions of mean ICP, mean CPP, mean Mx, and Mxa (Fig. 1) support a high, exponential increase in mortality with ICP above 20 mmHg and more gradual, linear relationship between outcome and autoregulation.

A simple evaluation of the rate of unfavorable outcome versus mean value of Mx (Fig. 2) shows that the rate of unfavorable outcome is a monotonically increasing function of Mx with an obvious threshold between Mx values of 0.2 and 0.4.

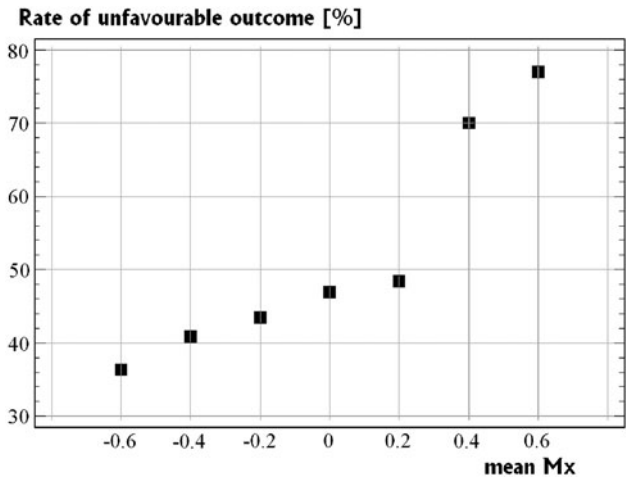

Fig. 2 The rate of unfavorable outcome increases along with average Mx

Mx was significantly correlated with Mxa ($r = 0.78$, $P < 0.001$). Mxa was on average greater than Mx (mean 0.01, SD ±0.29 vs. 0.20, ±0.22; $P < 0.001$). Mx and Mxa were both inversely correlated with Glasgow Outcome Score (Spearman's $R = -0.2$, $P < 0.01$ and $R = -0.15$, $P = 0.01$, respectively).

The results of the chi-square analysis for all patients are shown in Fig. 3a and b. The maximum chi-square values for unfavorable/favorable outcome (11.4) were greater than those for death and survival (6). The maximum chi-square

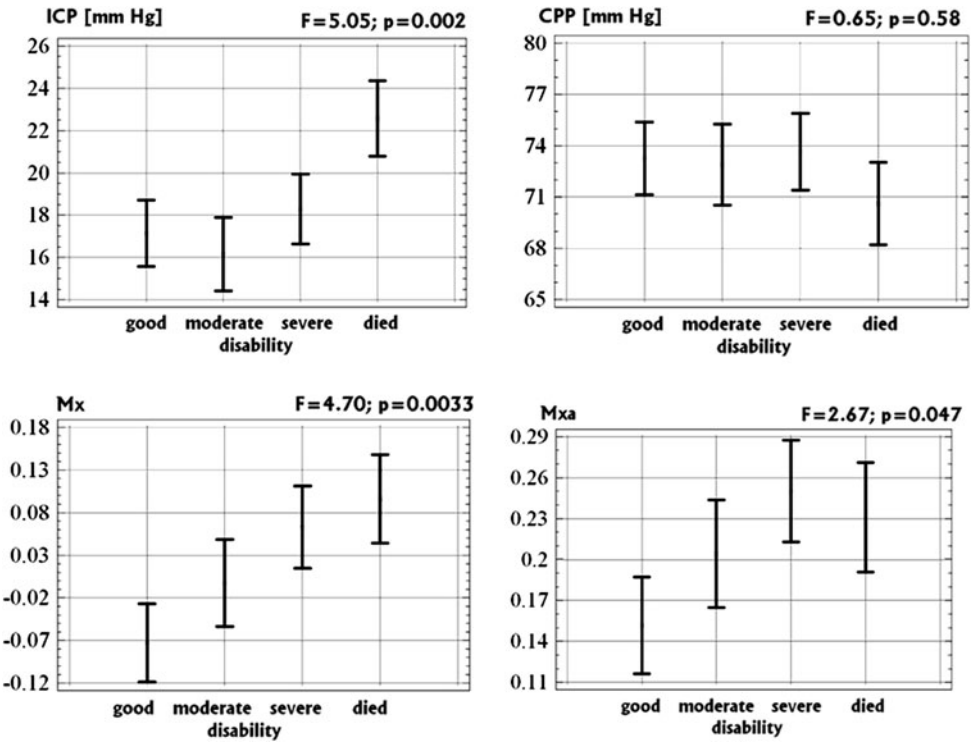

Fig. 1 Average values of ICP, CPP, Mx, and Mxa across outcome groups

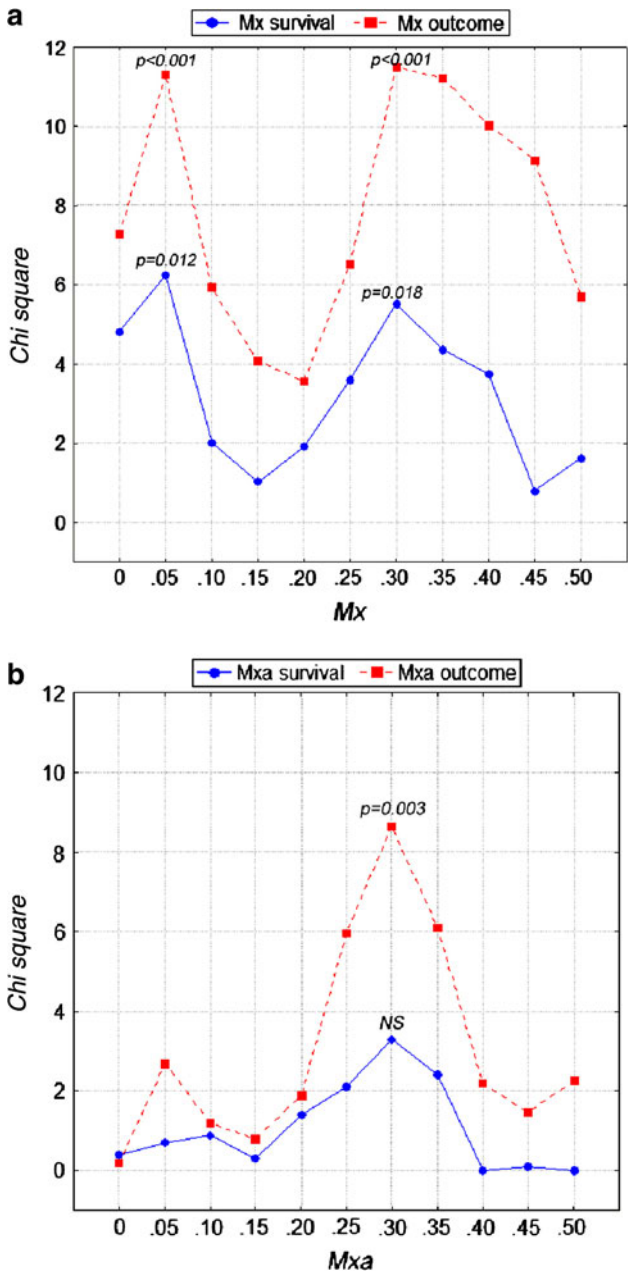

Fig. 3 **a** Graph showing chi-square values for survival (*squares*) and favorable outcome (*circles*) for Mx with their *P* values. **b** Graph showing chi-square values for survival (*squares*) and favorable (*circles*) outcome for Mxa with *P* value. *NS* not significant

for favorable outcome was greater for Mx (11.4) than for Mxa (8.7), suggesting that Mx is a better discriminator of outcome than Mxa.

The chi-square for favorable/unfavorable outcome and mortality discrimination demonstrated two distinctive peaks: at 0.3 and 0.05. The distribution of chi-square for Mx demonstrated one dominant peak at a value of 0.3. Sensitivity and specificity of outcome prediction for these thresholds are given in Tables 1 and 2.

Table 1 Physiologic data of the patients

Number of patients	248
Males	195 (79%)
Age years (median, IQR)	28 (22)
Admission GCS (median, IQR)	6 (4)
Glasgow Outcome Score (median, IQR)	4 (2)
ABP mmHg (mean, SD)	80.90 (±27.50)
CPP mmHg (mean, SD)	72.37 (±13.05)
ICP mmHg (mean, SD)	18.42 (±10.16)

Discussion

Very early studies indicated that cerebral autoregulation may be a strong discriminant of outcome following head injury [18–21]. Several decades later, this subject is still open to investigation, taking advantage of availability of new, more precise and feasible methods for continuous monitoring. Transcranial Doppler ultrasonography is one of such methods: it is non-invasive, cheap, and accurate.

Our results confirm the previously reported [9] association between the two transcranial Doppler-derived indices (Mx and Mxa) and outcome after head injury. Previously, a threshold of 0.3 had been indicated for Mx [8, 10]. Our findings suggest that it appears more appropriate to define two thresholds for Mx, a lower one (0.05) below which the likelihood of survival and favorable outcome are high and an upper one (0.30) above which there is a high likelihood of mortality and unfavorable outcome. The prognostic significance of intermediate values for Mx is smaller. On the contrary, chi-square values for Mxa show only one clear peak for favorable outcome, and no significant result for mortality. It is to be noted that the predictive value of both Mx and Mxa is higher for favorable outcome than for survival, unlike most other predictive indices like mean ICP or pressure-reactivity index [22]. Mx and Mxa are distributed uniformly between outcome groups (see Fig. 1). Mathematically, such a distribution will maximize the statistical difference between more equal groups (favorable and unfavorable patients break up roughly 50:50, while survived: died: 75:25). Mx is associated with outcome more strongly than Mxa, which confirms previous observations [9].

The practical problem with the Mx/Mxa indices is that, even though it can be used for monitoring, it requires continuous focusing of the ultrasound probes on the MCA. Keeping them in a fixed place in a Neuro Critical Care setting is very difficult and requires the continuous presence of an operator. On the other hand, TCD examination is non-invasive, cheap, and the pattern of MCA FV is very distinctive, enabling immediate detection of faulty recordings. Once that self-focusing probes are designed,

Table 2 Numeric thresholds for Mx and Mxa with sensitivity and specificity

	Lower threshold Mx	Sensitivity and specificity for lower threshold Mx (%)	Upper threshold Mx	Sensitivity and specificity for upper threshold Mx (%)	Threshold for Mxa	Sensitivity and specificity for Mxa threshold (%)
Survival	0.05	84	0.30	36	NS	NA
		29		81		
Favorable outcome	0.05	62	0.30	71	0.30	60
		60		57		82

NS not significant, *NA* not applicable

this technique of continuous monitoring of cerebral autoregulation will gain major importance in neurocritical care.

New technologies, based on the pressure-reactivity index [23], although invasive, provide information indirectly related to cerebral autoregulation continuously, allowing optimization of a CPP-oriented therapy [22] or early warning against refractory hypertension [10]. Recently, a new technology based on Near Infrared Spectroscopy (non-invasive) has been described [24, 25].

Limitations

In these patients we did not monitor intensity of treatment, particularly level of sedation.

It is true that higher ICP or low CPP most probably implicated more aggressive measures, including sedation. In most cases propofol was used (2–4 mg/kg/h) which is not supposed, unless used in large doses (6–8 mg/kg/h) to affect autoregulation or vascular reactivity [26]. Periods with intentionally shallow sedation (to assess neurological status or attempted weaning from ventilator) were excluded from the material. The reason is that TCD recording in such periods tends to be heavily disturbed.

We do not hold exact data on PaCO2 at the time of TCD examination for all recordings. In all patients mild hypocapnia or normocapnia was used (4–5 kPa). We previously studied the effect of a planned change in PaCO2 [27] on the Mx index in a subgroup of this population. The results were dramatically different from the effects we can find in volunteers [28]—change in PaCO2, on average less than 1 kPa (from normocapnia to mild hypocapnia), does not alter average Mx. Periods of weaning from ventilator, when PaCO2 can rise in an uncontrollable manner, similarly to periods of shallow sedation were excluded from the analysis.

In this study we did not analyze whether autoregulation indices were consistent over subsequent days of recording. This point has been partially addressed in an early study devoted to Mx 8. In patients with favorable outcome, the time-profile of Mx was uniform. In patients with unfavorable outcome Mx was greater, but the difference was more significant during the first 2 days after injury, suggesting that on average not secondary but rather primary dysautoregulation may have a stronger implication for outcome.

Conclusion

Transcranial Doppler-derived indices of autoregulation Mx and Mxa both appear to hold predictive value with special regard to favorable outcome, and studies on a larger sample population would elucidate whether these thresholds can be applied to all patients or only to a subset of them.

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