Impaired autoregulation is associated with mortality in severe cerebral diseases

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Special Issue on Neurosonology and Cerebral Hemodynamics

Abstract

Background: Small cerebral vessels respond to variations of cerebral perfusion pressure (CPP) by changes of vessel diameter inducing changes of blood flow resistance and keeping cerebral blood flow constant. This mechanism is called cerebral autoregulation (CA). An index Mx, observing correlation between cerebral blood flow velocity (CBFV) and CPP has been recently introduced for assessment of state of CA during spontaneous changes of CPP. In the current study, the relationship between lethal outcome during hospitalization and Mx index was investigated.

Methods: Thirty patients (18-77 years, mean 53±16 years) with severe cerebral diseases were studied. CBFV, arterial blood pressure (ABP) and intracranial pressure (ICP) were simultaneously recorded. Assessments were repeated at days 2, 4 and 7. Mx was calculated retrospectively, as averaged correlation between CBFV and CPP (=ABP-ICP). Positive values of Mx indicated impairment of CA.

Results: Six of the patients died in-hospital. In this group Mx was significantly higher than in the group of survivors (0.28±0.40 versus 0.03±0.21; p<0.05). Changes of Mx during days of monitoring (Mx last day - Mx first day) were not significantly related to mortality. Nine patients showed an Mx >0.2, four of them died, whereas from the 21 patients with Mx <0.2 only two died. The association between increased Mx and death was significant (p<0.05, Fisher’s exact test). Mx correlated significantly with Glasgow Outcome Score (GOS) in the subgroup of patients with known GOS (N=21; R=-0.56, p<0.05).

Conclusion: Increased Mx indicates impairment of CA and is associated with risk of death in patients with severe cerebral diseases.

Keywords: Cerebral autoregulation, Cerebral perfusion pressure, Intracranial pressure, Cerebral disease.
Introduction

The mechanism of cerebral autoregulation (CA) minimizes variation of cerebral blood flow (CBF) during changes of cerebral perfusion pressure (CPP). Pressure excited dilatation or constriction of small arteries regulates cerebral blood flow resistance and prevents the brain from ischemia during decrease of CPP, as well as from hyperemia during increase of CPP.

Severe cerebral diseases may affect cerebral autoregulation [1, 2] and cause vulnerability of the brain. Therefore, the monitoring of cerebral autoregulation provides important information for patient treatment. Various CA monitoring methods have been introduced so far. They generally rely on the analysis of cerebral blood flow velocity (CBFV) either during controlled induction of pressure changes [3, 4] or during spontaneous oscillations of arterial blood pressure (ABP) or CPP [5-8]. In a former study with traumatic brain injured (TBI) patients [5] an index (so-called Mx index) has been introduced, which evaluated state of CA during spontaneous changes of CPP and corresponded to clinical outcome. In patients with intracranial pressure (ICP) monitoring, Mx was calculated from correlation between CBFV and CPP. In patients without ICP monitoring an iterative, self-adjusting method of non-invasive ICP assessment could be used for estimating CPP and Mx [9].

Several recent studies reported an association between unfavorable clinical outcome and increased values of Mx in patients with TBI [5, 10, 11], intracerebral hemorrhage [12], and ischemic stroke [13]. In the current study the association between Mx and lethal outcome during hospitalization in a population of diverse cerebral diseases (TBI, hemorrhagic and ischemic stroke, and others) was investigated.

Methods

Patient population

In a retrospective study, signal data of thirty patients with severe cerebral diseases (age 18–77 years, mean 53±16 years, 20 male/10 female) were analyzed. Patients were treated in Chemnitz Medical Centre between 2006 and 2008. The patients suffered from TBI (n=15), subarachnoidal hemorrhage (n=9: traumatic n=5, spontaneous n=4), MCA infarction (n=2), intracerebral hemorrhage (n=11: traumatic n=3, spontaneous n=8), intracranial hematoma (n=9), sinus venous thrombosis, hypoxic encephalopathy, and encephalitis.

At the time of data recording, all the patients were sedated, paralyzed, and mechanically ventilated. Their arterial partial pressure of CO₂ (PaCO₂) ranged from 30–35 mmHg. During signal recording, ventilator settings were unchanged in order to keep PaCO₂ constant.

Monitoring

Transcranial Doppler (TCD) measurements were taken using 2 MHz pulsed Doppler device (Multidop-P, DWL, Sipplingen, Germany). The envelope curve of CBFV in the middle cerebral artery (MCA) was continuously recorded in the hemisphere ipsilateral to brain lesion in most cases. The ultrasound probe was fixed mechanically with a holder frame or elastic headband. TCD recording was performed during stable periods free from nursing, physiotherapy, or tracheal suction. The clinical objective of recording was to assess the state of cerebral autoregulation [5].

ABP was measured with a standard manometer line inserted into the radial artery. ICP was measured using either implanted intraparenchymal or intraventricular microsensors (Raumedic GmbH, Helmbrechts, Germany).

Computer-assisted recording

Personal-assisted recording systems (Daq 112B, Iotech, Inc., Cleveland, OH, USA) and home written software [14] were used for recording and analyzing CBFV, ABP, and ICP signals. Sampling frequencies ranged from 25 Hz to 50 Hz. Signals were assessed during 60 minutes. If possible, recording was repeated at days 2, 4, and 7. Signal data was recorded initially at day 1 from all 30 patients (34 recordings), at day 2 from 28 patients (33 recordings), at day 4 from 19 patients (21 recordings) and at day 7 from 7 patients (8 recordings). In total 96 recordings of 30 patients were acquired.

Assessment of cerebral autoregulation

Recorded signal data of CBFV, ABP, and ICP was initially filtered by a 0.15 Hertz low-pass filter in order to erase oscillations from breathing. Cerebral autoregulation was assessed in terms of Pearson’s correlation coefficients of 60 consecutive samples (in steps of 5 seconds) of CBFV and CPP (=ABP-ICP) values, i.e. during 5-minute periods. These correlation indices were averaged, and resulted in the autoregulation index Mx [5]. Essentially being a correlation coefficient, Mx may take on every value between -1.0 and 1.0. In case of active CA, small cerebral arteries constrict during increase of CPP and dilate during decrease of CPP. That way, changes of CBF resistance compensate or even over-compensate the CPP change, which means that CBFV and CPP are not correlated or are negatively correlated, i.e. Mx becomes zero or negative. In case of impaired CA, CBFV passively follows changes of CPP, i.e. Mx becomes positive.

One Mx value was calculated for each signal recording. If related to a patient, Mx means the average Mx over all recordings of this patient. For dichotomous analysis of CA and survival a cut-off point of Mx above or below 0.2 was used.

All signal monitoring was part of a clinical routine and did not require individual consents. Local ethical committee approved this study.

Results

Six of the patients died during their hospitalization. Mean age (± SD) in this group (Non-Survivors) was 53±12 years,
while mean age of the remaining 24 patients (Survivors) was 51±16. The difference of age in both groups was not significant (p=0.23).

Mx was significantly higher (p<0.05; students t-test) in the Non-Survivors group than in the Survivors group (0.28±0.40 versus 0.03±0.21). Figures 1 and 2 present signal recordings from a patient in the non-survivors and a patient in the survivors group, respectively. Change of Mx during consecutive days of monitoring (i.e. Mx last day - Mx first day) was not significantly related to mortality (Non-Survivors: 0.14±0.35 versus Survivors: -0.17±0.38; p=0.17). Nine patients showed an Mx >0.2, four of them died, while in 21 patients Mx was <0.2, only two of them died (Table 1). This association between high Mx and mortality was significant (p<0.05; OR=7.6). In 21 patients, the 3-month Glasgow Outcome Score (GOS) could be assessed. In this subgroup, Mx significantly correlated with GOS (R=-0.56, p<0.05). Figure 3 illustrates the correlation between Mx and GOS. In fourteen patients craniotomy was performed. Craniotomy was neither related to Mx (p=0.42) nor was it related to mortality (p=0.12).

**Discussion**

The results showed a moderate but significant association between increased Mx (indicating impairment of CA) and mortality during hospitalization. In addition a relationship between increased Mx index and GOS could be found, i.e. a decline of CA was related to poor clinical outcome. Mortality was neither associated with age nor with craniotomy intervention. A relationship between increased Mx and worse clinical outcome in TBI patients was shown in former studies [5]. Recently an association between unfavorable outcome and secondary increase of Mx in patients with intracerebral hemorrhage was reported [12]. In our study, an association between increased Mx and mortality could be stated in a population with diverse types of cerebral diseases including TBI as well as hemorrhagic and ischaemic stroke. But there was no significant association between secondary increase of Mx and mortality in our

**Table 1. Relationship between Mx and mortality during hospitalisation.**

| Mx > 0.2 | 4 | 5 | 9 |
| Mx < 0.2 | 2 | 19 | 21 |
| Sum       | 6 | 24 | 30 |

In 9 patients Mx was on average higher than 0.2 (upper line). Four of these patients died. In the group of 21 patients Mx below 0.2, only two patients died (lower line). Mortality was significantly higher in patients with high Mx, i.e. Mx>0.2 (p<0.05; Odds Ratio [OR] =7.6).

**Figure 1.** Signal recording of a 74 year-old patient with spontaneous subarachnoidal hemorrhage who died during hospitalization. CBFV, ABP, and ICP have been recorded for one hour, CPP has been calculated by means of ABP-ICP. CBFV (upper channel) and CPP (middle channel) signals have been filtered and Mx calculated (lower channel). The circles show the calculated correlation coefficients between CBFV and CPP. The curve is the moving average of five consecutive correlation coefficients. The Mx value related to this recording is 0.61 and was calculated as average over all correlation coefficients of this recording. This value corresponds to the optical impression of parallel curves of CPFV and CPP.
Figure 2. Signal recording of a 34-year-old patient with traumatic brain injury, part of the group of survivors, with unknown GOS. Signal processing was same as described under Fig. 1. CBFV (upper channel) and CPP (middle channel) signals have been filtered and Mx calculated (lower channel). The Mx value is -0.20 and was calculated as average over all correlation coefficients of this recording.

a) CBFV, CPP and Mx curves over the whole 1-hour time period.

b) CBFV, CPP and Mx curves during a 400-sec time subinterval. This graph clearly shows anti-parallel oscillations of CBFV and CPP, which correspond to a negative correlation between both curves.
study. Especially in the Non-Survivors group Mx showed a high variation (SD=0.40). However, it remains unclear whether this can be explained by the heterogeneity of the population or whether high variability is an intrinsic property of this index.

Our choice of 0.2 as a critical threshold for increased Mx was somewhat arbitrary. However, its interpretation as an indicator of reduced CA was justified by its prognostic potential for outcome prognosis. In a recent study (Sorrentino et al., 2011 [11]) an Mx value of 0.3 was proposed to be the critical threshold for disturbed CA in TBI patients.

Only for 21 patients, we had access to a detailed GOS index. It cannot be ruled out that this might have yielded a bias in this sub-group. One obvious effect was the predominance of fatal outcome during hospitalization, because all fatal cases were registered. However, this could have only affected the analysis of correlation between GOS and Mx. In all other investigations, we restricted on a dichotomous classification of outcome into survival and non-survival. This study was based on a relatively small population of 30 patients. Especially in view of the inclusion of diverse types of cerebral diseases, it would be appropriate to conduct further studies with larger populations. Moreover, a larger population would also allow the analysis of specificity of this index.

It is not clear whether Mx was an independent predictor of clinical outcome. Investigation of a possible relationship between Mx and other clinical predictors was not subject of this study.

Conclusions

Reduced CA with Mx >0.2 is significantly related to lethal outcome in patients with severe cerebral diseases. Increased Mx also corresponds to worse 3-month clinical outcome. Further studies with larger populations and complete outcome information would be appropriate.

Abbreviations

ABP: Arterial blood pressure; CA: Cerebral autoregulation; CBF: Cerebral blood flow; CBFV: Cerebral blood flow velocity; CPP: Cerebral perfusion pressure; GOS: Glasgow outcome score; ICP: Intracranial pressure; MCA: middle cerebral artery; PaCO2: Partial pressure of CO2; TBI: Traumatic brain injury; TCD: Transcranial Doppler

Acknowledgments

Dr. M. Czosnyka is on leave from Warsaw University of Technology, Poland.

Competing interests

The authors declare no conflict of interest.

References