

Cerebrovascular Pressure Reactivity and Cerebral Oxygen Regulation After Severe Head Injury

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Abstract

Background To investigate the relationship between cerebrovascular pressure reactivity and cerebral oxygen regulation after head injury.

Methods Continuous monitoring of the partial pressure of brain tissue oxygen ($P_{br}O_2$), mean arterial blood pressure (MAP), and intracranial pressure (ICP) in 11 patients. The cerebrovascular pressure reactivity index (PRx) was calculated as the moving correlation coefficient between MAP and ICP. For assessment of the cerebral oxygen regulation system a brain tissue oxygen response (TOR) was calculated, where the response of $P_{br}O_2$ to an increase of the arterial oxygen through ventilation with 100 % oxygen for 15 min is tested. Arterial blood gas analysis was performed before and after changing ventilator settings.

Results Arterial oxygen increased from 108 ± 6 mmHg to 494 ± 68 mmHg during ventilation with 100 % oxygen. $P_{br}O_2$ increased from 28 ± 7 mmHg to 78 ± 29 mmHg, resulting in a mean TOR of 0.48 ± 0.24 . Mean PRx was 0.05 ± 0.22 . The correlation between PRx and TOR was $r = 0.69$, $P = 0.019$. The correlation of PRx and TOR with the Glasgow outcome scale at 6 months was $r = 0.47$, $P = 0.142$; and $r = -0.33$, $P = 0.32$, respectively.

Conclusions The results suggest a strong link between cerebrovascular pressure reactivity and the brain's ability to control for its extracellular oxygen content. Their simultaneous impairment indicates that their common actuating element for cerebral blood flow control, the cerebral resistance vessels, are equally impaired in their ability to regulate for MAP fluctuations and changes in brain oxygen.

Keywords Brain tissue oxygen · Neuromonitoring · Brain tissue oxygen response · Cerebrovascular pressure reactivity · Head injury · Autoregulation

Introduction

The human brain has several mechanisms for regulation of cerebral blood flow (CBF). One of these physiological mechanisms, the cerebral oxygen regulation system, is thought to protect the brain from very high and potentially “toxic” oxygen concentrations by decreasing CBF and thus oxygen delivery. This phenomenon was first recognized in the pioneering work on CBF measurements by S. S. Kety and C. F. Schmidt [1] from 1948, when they described a 13 % reduction of CBF in healthy volunteers breathing 85–100 % oxygen. These effects of hyperoxia on CBF have since been repeated using various methods for CBF assessment in healthy subjects [2–4] and similar CBF reductions have also been described in head injury [5].

However, little is known about the relationship of the cerebral oxygen regulation system with other mechanisms of CBF regulation, in particular cerebrovascular pressure autoregulation [6]. We therefore analysed the relationship between the oxygen regulation system and cerebrovascular

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pressure reactivity in patients after severe head injury. Cerebrovascular pressure reactivity is a key factor for pressure autoregulation. We hypothesized that the cerebral oxygen regulation system and cerebrovascular pressure reactivity are synchronously impaired after head injury. This hypothesis was based on the assumption that the cerebrovascular resistance vessels, which constitute their common actuating element, provide the CBF regulating capacity for both systems. We tested this hypothesis by performing brain tissue oxygen response testing (TOR) and simultaneous prolonged recordings of the cerebrovascular pressure reactivity index (PRx).

Methods

We prospectively studied 11 patients with severe traumatic head injury. Mean age was 42 years (range 18–82 years), median Glasgow Come Score was 4 (range 3–6) [7], and 5 were female. Computerized tomography findings were classified according to Marshall et al. [8] and 5 patients had diffuse injury type II, 2 had diffuse injury type III, 1 had diffuse injury type IV, and 3 had evacuated mass lesions. Patients were admitted to the neurosurgical intensive care unit of Leipzig University Hospital.

All patients required continuous sedation and artificial ventilation. Ventilation was set to aim for partial pressure of arterial oxygen (P_{aO_2}) of 100–120 mmHg and partial pressure of arterial carbon dioxide (P_{aCO_2}) of 35–40 mmHg. Blood gases were checked every 8 h or as clinically indicated.

Treatment targeted intracranial pressure (ICP) below 20 mmHg by nursing patients with 30-degree head elevation. Periods of elevated ICP were treated with bolus infusions of Mannitol or 10 % hypertonic saline. Hemodynamic augmentation with volume expansion and/or vasopressors was used to keep cerebral perfusion pressure (CPP) at 60–70 mmHg. Space occupying hematomas were surgically evacuated.

Clinical outcome was assessed 6 months after trauma by one of the authors (M. J.) using the Glasgow Outcome Scale (GOS) by personal follow-up examination or telephone interview with the patient or caregiver [9].

Neuromonitoring

As part of the routine neuromonitoring in severe head injury, patients had continuous monitoring of mean arterial pressure (MAP), ICP, and the partial pressure of brain tissue oxygen (P_{brO_2}). MAP was monitored by a catheter inserted into the radial or femoral artery and the pressure transducer referenced to the Foramen of Monro (DTXPlus,

Becton–Dickinson Infusion Therapy Systems Inc., Franklin Lakes, NJ). ICP and P_{brO_2} were monitored with intraparenchymal probes (Codman Microsensors ICP transducers, Codman & Shurtleff Inc., Raynham, MA; Licox CC1.SB, Integra NeuroSciences Inc., Plainsboro, NJ), inserted via a double lumen skull bolt (Licox IM2, Integra NeuroSciences Inc., Plainsboro, NJ) into the frontal white matter of the more severely injured hemisphere on CT. The probes were placed in normal appearing brain on CT, which was confirmed using routine follow-up imaging.

Analog data of MAP, ICP, and P_{brO_2} were sampled at 30 Hz from the bedside monitors, processed through an analog-to-digital converter (Licox MMM, Integra NeuroSciences, Plainsboro, NJ), and recorded by a portable bedside computer using ICM-plus software (ICM-plus, Cambridge University, Cambridge, UK). Cerebral perfusion pressure (CPP) was calculated as the difference of MAP–ICP. Mean values of MAP, ICP, CPP, and P_{brO_2} were stored every 30 s. Artefacts caused by temporary disconnection from monitors were manually eliminated from the data sets.

The Ethics Committee of Leipzig University approved continuous computerized neuromonitoring and this study.

Brain Tissue Oxygen Response

To test the cerebral oxygen regulation system, we calculated the brain tissue oxygen response (TOR) according to van Santbrink et al. [10]. Please see the equation for calculation of TOR in the “Appendix section”. In brief, baseline measurements of P_{brO_2} and P_{aO_2} were taken. This was followed by a 15 min period of ventilation with a fraction of inspired oxygen (F_iO_2) of 1.0 (oxygen challenge). At the end of the 15 min oxygen challenge P_{brO_2} and P_{aO_2} were measured again, before the ventilator settings were returned to baseline. High TOR values indicate impaired cerebral oxygen regulation, when P_{aO_2} increases lead to very high, possibly “unphysiologic” P_{brO_2} increases. Low TOR values stand for intact cerebral oxygen regulation.

We performed two oxygen challenges per patient 24–48 h apart after patients were hemodynamically stabilized and a P_{brO_2} probe run-in time of approximately 12–24 h after insertion.

Cerebrovascular Pressure Reactivity Index

The cerebrovascular pressure reactivity index (PRx) was calculated as previously described by Czosnyka et al. [11] as a moving Pearson’s correlation coefficient between 30 consecutive samples of MAP and ICP averaged over 10 s, thus incorporating data from 300 s. PRx values from overlapping epochs were stored every 30 s. PRx uses

changes in cerebral blood volume, which are the response of the cerebral resistance vessels to slow waves of arterial blood pressure and can be measured with the ICP signal, to quantify the reactivity of these resistance vessels. A high PRx indicates impaired cerebrovascular reactivity, whereas PRx around zero indicates intact reactivity.

Data Analysis

Mean values of TOR, $P_{br}O_2$, P_aO_2 and the partial pressure of arterial carbon dioxide (P_aCO_2) taken before (baseline) and at the end of each 15 min oxygen challenge were calculated for each patient. Parameters at baseline and at the end of the oxygen challenge were compared using non-parametric Wilcoxon-matched-pairs analysis. For the purpose of this study we calculated mean PRx over the 12 h period before each oxygen challenge, because PRx needs to be averaged over longer periods to obtain a reliable assessment of the status of cerebrovascular pressure reactivity, while PRx-snapshots are of limited value. Correlation between parameters was calculated using non-parametric Spearman coefficient. The probability of a Type 1 error (α) of 5 % was accepted as being statistically significant.

Results

The first oxygen challenge was performed on average 57 h after trauma (range 15–123 h), the second oxygen challenge 26 h after the first (range 16–123 h). One patient had only one oxygen challenge.

The mean $P_{br}O_2$ at baseline was 28.7 mmHg (range 15.2–37.3 mmHg), the mean P_aO_2 was 107.8 mmHg (range 96.8–115.5 mmHg). Ventilation with a F_iO_2 of 1.0 for 15 min significantly increased $P_{br}O_2$ to 78.7 mmHg (range 30.0–135.5 mmHg; $P = 0.003$) and P_aO_2 to 494 mmHg (range 353–576 mmHg; $P = 0.003$). This resulted in an average TOR of 0.48 (range 0.05–0.91).

The average P_aCO_2 at baseline was 37.0 mmHg (range 32.6–40.7 mmHg), and at the end of the oxygen challenge remained at 36.9 mmHg (range 31.4–42.2 mmHg, $P = 0.92$). During the oxygen challenge average MAP was 86.3 mmHg (range 64.2–114.6 mmHg), ICP was 13.7 mmHg (range 5.1–28.8 mmHg), and CPP was 72.8 mmHg (range 52.8–86.8 mmHg).

Mean PRx over the 12 h before the oxygen challenge was 0.05 (range –0.26 to 0.45). We found a significant correlation between TOR and PRx of $r = 0.69$, $P = 0.019$ (Fig. 1). The correlation between TOR and $P_{br}O_2$ at baseline was $r = 0.06$, $P = 0.87$, indicating no effect of baseline $P_{br}O_2$ on TOR.

The correlation between TOR and average ICP during the oxygen challenge was $r = 0.07$, $P = 0.83$; and between

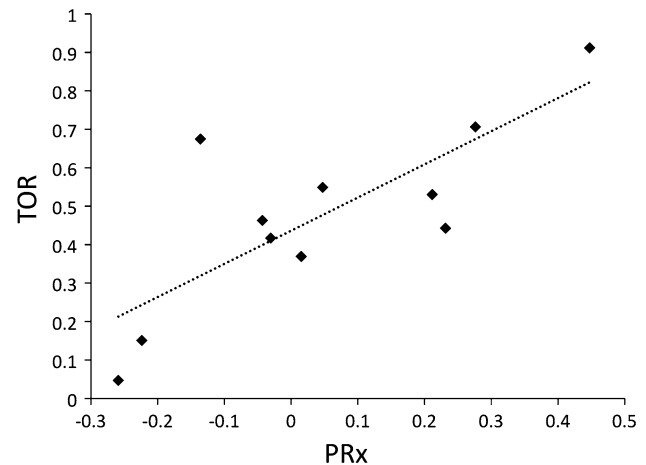


Fig. 1 Relationship between the index of cerebrovascular pressure reactivity, PRx, and the brain tissue oxygen response, TOR. The Spearman correlation coefficient is $r = 0.69$, $P = 0.019$. The dotted line is the linear regression function

TOR and average CPP during the oxygen challenge was $r = -0.13$, $P = 0.71$.

The median GOS at 6 months was 3 (range 1–4). The correlation between TOR and GOS was $r = -0.33$, $P = 0.32$. The correlation between PRx and GOS was $r = -0.47$, $P = 0.14$.

Discussion

This study investigated the relationship between the cerebral tissue oxygen response, TOR, and cerebrovascular pressure reactivity index, PRx, in patients after head injury. We found a significant correlation between TOR and PRx, supporting our hypothesis that both CBF regulating systems were simultaneously impaired after trauma. The results further suggest that the common actuating element for both systems, the cerebral resistance vessels, is equally impaired in its ability to control CBF in response to blood pressure fluctuations and changes in P_aO_2 . This failure of CBF control is graded and both indexes, TOR and PRx, are likely to provide similar information regarding the degree of impairment.

It has been debated whether the higher TOR values associated with unfavorable neurological outcome are the result of impaired vasoreactivity or are the appropriate physiological response to ischemia [6]. We believe that our study results point toward underlying vasomotor paralysis, as impaired (i.e., passive) cerebrovascular reactivity, indicated by high PRx, was associated with high TOR. In a potential scenario where high TOR indicates an active physiological response to ischemia, one would expect that this should have been associated with low PRx, suggesting preserved active cerebrovascular regulation. Also, baseline $P_{br}O_2$ levels had no influence on TOR,

meaning that lower $P_{br}O_2$ did not lead to higher or lower TOR in the population studied.

A limitation of our study is the small sample size. However, we do not believe that the significant correlation between TOR and PRx will change substantially with larger patient numbers. The correlation between clinical outcome and TOR and PRx is likely to become better defined, which has been described in previous studies using larger cohorts [10, 12]. TOR provides a local measurement only and the oxygen challenge might yield different TOR values in other areas of the brain, in particular on the contralateral side or in lesional/perilesional tissue. In abnormal tissue, both higher and lower $P_{br}O_2$ changes with an oxygen challenge, as compared to normal tissue, have been reported, suggesting a variable response [13, 14]. This variable response is likely dependent on CBF around the probe, with very low CBF resulting in “falsely” low TOR [15].

Treatment of acute brain injury with hyperoxia, both normobaric and hyperbaric, has gained interest through encouraging study results, reporting beneficial effects on both cerebral metabolic parameters and outcome in experimental and clinical studies [16–18]. Based on the assumption that the brain has active mechanisms to control and compensate for potentially harmful supraphysiologic oxygen concentrations, the practice of treating brain injury with hyperoxia needs to be reconsidered. Monitoring of cerebrovascular function, either through TOR or, as more commonly performed, PRx, might help to identify patients with the potential to benefit from hyperoxic treatment. On the one hand, intact vasoreactivity has the potential to provide better control against “toxic” $P_{br}O_2$ levels. On the other hand, patients with impaired vasoreactivity are at higher risk of cerebral ischemia and might thus be better treated with supraphysiologic oxygen supply. Based on the current evidence, however, it remains to be determined if the potentially “toxic” effects of high oxygen levels, poorly controlled in the presence of cerebral vasoparalysis, prevail over the potential benefits of bringing oxygen to the ischemic/hypoxic brain. Ultimately, only well-designed clinical trials will be able to answer this important question.

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Conflict of interest Matthias Jaeger has no conflicting interests to declare. Erhard W. Lang is a member of the Integra Speakers Bureau and consults Integra for complaints received with the use of Licox probes.

Appendix

Equation for calculation of the Tissue Oxygen Response (TOR), where $\Delta P_{br}O_2$ and ΔP_aO_2 are the differences of the

respective values at baseline and at the end of the 15 min oxygen challenge:

$$TOR = \frac{\Delta P_{br}O_2}{\Delta P_aO_2} \times \frac{1}{P_{br}O_2(\text{baseline})} \times 100 \%$$

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