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ORIGINAL ARTICLE

Should the Neurointensive Care Management of Traumatic Brain Injury Patients be Individualized According to Autoregulation Status and Injury Subtype?

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Abstract
Introduction The status of autoregulation is an important prognostic factor in traumatic brain injury (TBI), and is important to consider in the management of TBI patients. Pressure reactivity index (PRx) is a measure of autoregulation that has been thoroughly studied, but little is known about its variation in different subtypes of TBI. In this study, we examined the impact of PRx and cerebral perfusion pressure (CPP) on outcome in different TBI subtypes.
Methods 107 patients were retrospectively studied. Data on PRx, CPP, and outcome were collected from our database. The first CT scan was classified according to the Marshall classification system. Patients were assigned to "diffuse" (Marshall class: diffuse-1, diffuse-2, and diffuse-3) or "focal" (Marshall class: diffuse-4, evacuated mass lesion, and non-evacuated mass lesion) groups. 2 × 2 tables were constructed calculating the proportions of favorable/unfavorable outcome at different combinations of PRx and CPP.
Results Low PRx was significantly associated with favorable outcome in the combined group ($p = 0.002$) and the diffuse group ($p = 0.04$), but not in the focal group ($p = 0.06$). In the focal group higher CPP values were associated with worse outcome ($p = 0.02$). In diffuse injury patients with disturbed autoregulation (PRx >0.1), CPP >70 mmHg was associated with better outcome ($p = 0.03$).
Conclusion TBI patients with diffuse injury may differ from those with mass lesions. In the latter higher levels of CPP may be harmful, possibly due to BBB disruption. In TBI patients with diffuse injury and disturbed autoregulation higher levels of CPP may be beneficial.

Keywords Cerebral perfusion pressure · Cerebrovascular pressure autoregulation · Head injury · Outcome

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Introduction

The brain is dependent on a continuous supply of oxygenated, nutrient-rich blood. The process of keeping an adequate cerebral blood flow (CBF), despite variations in both systemic blood pressure and cerebral metabolic requirements, is referred to as cerebral autoregulation [1]. The direct mechanism is changes in cerebrovascular resistance by vasoconstriction and dilatation, orchestrated by an interplay of different mediators [2].

One key element of cerebral autoregulation is cerebral pressure reactivity, the response of smooth vascular muscle to changes in systemic blood pressure. In normal pressure reactivity, an increase in arterial blood pressure (ABP) will evoke a compensatory vasoconstriction and hence an increase in cerebrovascular resistance, keeping the CBF stable [3]. In traumatic brain injury, the normal process of pressure reactivity may be more or less disturbed, which increases the brain's vulnerability to potentially harmful events of hypoperfusion or hyperemia. When we studied the impact of different CPP management strategies on outcome, the patients responded differently depending on status of pressure reactivity [4]. The status of autoregulation is thus important and should be taken into account in the management of the TBI-patient, as pointed out in the Brain Trauma Foundation's guidelines of 2007 [5].

When pressure reactivity is intact, increased ABP will cause cerebral vasoconstriction and hence a decrease in cerebral blood volume, accompanied by a decrease in

intracranial pressure; and vice versa. This relationship can be used to assess pressure reactivity. The pressure reactivity index (PRx) is calculated as the moving correlation coefficient between ABP and ICP based on spontaneous fluctuations in ABP [6]. PRx has in retrospective studies been shown to correlate strongly with outcome [2, 7]. Using PRx, "optimal" cerebral perfusion pressure for individual TBI patients can be determined retrospectively, with better outcome for patients treated at CPP levels close to their theoretical "optimum" [8]. However, PRx has so far been used more as a tool for research than clinical decision making, possibly due to the variable nature of the parameter [9].

The relation among PRx, CPP, and outcome has mostly been studied in heterogeneous patient groups, comprised of patients with diffuse injury, as well as intra- or extracerebral mass lesions [2, 7, 10]. Few studies have targeted pressure reactivity in relation to different types of head injury, and what impact PRx and CPP has on outcome in different injury types. The purpose of this work was to study pressure reactivity in different types of TBI, and to investigate the impact of pressure reactivity and CPP on outcome in different injury subtypes.

Materials and Methods

Patients and Treatment Protocol

We retrospectively studied 107 TBI patients admitted to the neurointensive care unit at Uppsala University Hospital between Jan 2008 and Feb 2011. Inclusion criteria were age >15 years and more than 8 h of valid recording time of ICP and ABP. Patients with previous TBI or cranial surgery were not included. The first CT scan was classified according to the Marshall CT classification system [11], see Table 1. Demographic data are presented in Table 2. ABP was measured invasively in the radial artery. ICP was measured by external ventricular drain (EVD) or by an intraparenchymal transducer. High-resolution physiological data were recorded by a multimodal monitoring system and stored for later analysis. Mean values of CPP and PRx for the first 96 h were calculated. Outcome was assessed by the extended Glasgow outcome scale (GOSE) [12, 13] after 6 months.

In case of CSF drainage, craniospinal compliance may be altered, and changes in ABP may not produce proportionally large changes in ICP. In this case, PRx may not be indicative of the true status of pressure reactivity. To avoid this, ICP data collected from an EVD were only used when the EVD was closed. In case of opening of an EVD, all data recorded after that time point were omitted. In a similar manner, data recorded after decompressive craniectomy, or after the initiation of pentobarbital coma was omitted since these treatments may influence PRx.

Table 2 Patients and groups characteristics

Patient characteristics	
Male [n (%)]	84 (78.5)
Female [n (%)]	23 (21.5)
Age (mean ± SD)	40.6 ± 20.2
Marshall group	
D1 [n (%)]	2 (1.9)
D2 [n (%)]	49 (45.8)
D3 [n (%)]	16 (15.0)
D4 [n (%)]	8 (7.5)
EML [n (%)]	5 (4.7)
NEML [n (%)]	27 (25.2)
Diffuse injury (D1–D3) [n (%)]	67 (62.6)
Focal injury (D4+EML+NEML) [n (%)]	40 (37.4)

SD Standard deviation, *D1* diffuse injury type 1, *D2* diffuse injury type 2, *D3* diffuse injury type 3, *D4* diffuse injury type 4, *EML* evacuated mass lesion, and *NEML* non-evacuated mass lesion

Table 1 Definitions of Marshall classes and abbreviations used in this paper

Abbreviation used in this paper	Category	Definition
D1	Diffuse injury I	No visible intracranial pathology seen on CT scan
D2	Diffuse injury II	Cisterns are present with midline shift 0–5 mm and/or: lesion densities present, no high- or mixed-density lesion >25 cc
		May include bone fragments and foreign bodies
D3	Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm. No high- or mixed-density lesion >25 cc.
D4	Diffuse injury IV (shift)	Midline shift >5 mm. No high- or mixed-density lesion >25 cc.
EML	Evacuated mass lesion	Any lesion surgically evacuated.
NEML	Non-evacuated mass lesion	High- or mixed-density lesion >25 cc not surgically evacuated.

All patients were treated according to a standardized protocol with the primary goals of keeping CPP >60 mmHg and ICP <20 mmHg. No active effort was made to raise CPP further than 60 mmHg. In case of systemic hypotension, clear fluids and colloids were administered, and thereafter vasopressors if needed. Expansive lesions were rapidly identified and evacuated. Elevated ICP was primarily treated with increased sedation, slight hyperventilation and CSF drainage if possible. Second line of treatment for intracranial hypertension was pentobarbital coma and/or decompressive craniectomy. Therapy with hyperosmotic diuretics, i.e., mannitol, was generally used only as an emergency measure to lower intracranial pressure immediately before other treatments, such as surgery to remove expansive lesions. Hypertonic saline was not used in this treatment protocol.

Pressure Reactivity and CPP

PRx was computed based on the ICP and ABP waveforms as the correlation of 30 contiguous averaged 10-s segments, with ICP on the Y-axis and ABP on the X-axis. The 5-min windows were moved through the patient data in increments of 12 s, generating 5 values per minute [14]. Then, the median value was selected for each minute of monitoring. To generate a summary measure for each patient, the mean of the minute by minute values over the monitoring time was calculated. Positive PRx values indicate impaired pressure autoregulation, while negative values or values close to zero indicate preserved pressure autoregulation.

Mean CPP values for the monitoring time were calculated for each patient.

Patient Groups and Statistics

The diffuse Marshall classes D1–D3 were classified together as the "diffuse" group, and D4 together with EML (evacuated mass lesion) and NEML (non-evacuated mass lesion) were classified as the "focal" group. Our aim was to separate patients with diffuse injuries from those with mass lesions. The distinction between these two categories according to the Marshall scale is not clear; classes D3 and D4 both include high or mixed-density lesions up to 25 cc [3], but in D4 cases a midline shift >5 mm should be present. To balance the division of borderline cases, D3 was included in the diffuse group and D4 in the focal group since the presence of a midline shift more resembles a focal injury with mass lesion. GOSE score was dichotomized into "unfavorable" (1–4) and "favorable" (5–8).

The differences in mean CPP and PRx between the unfavorable and favorable groups were assessed with Mann–Whitney U-test. Separate calculations were done for the diffuse and focal groups.

To investigate the impact of different levels of CPP in different status of autoregulation, patients were divided into groups based on thresholds of PRx and CPP. The PRx-groups were PRx <0.05, PRx between 0.05 and 0.1; and PRx >0.1. These thresholds were chosen based on the rational that PRx <0.05 signifies largely normal autoregulation, while PRx >0.1 signifies deranged autoregulation. In the intermediate group were patients with slightly to moderately disturbed autoregulation. A single CPP threshold (70 mmHg) was chosen to divide patients into groups with CPP <70 mmHg or CPP >70 mmHg. This level seems reasonable to divide patients into relative high-CPP and low-CPP groups since CPP >70 is a common goal in treatment protocols.

2 × 2 tables were then constructed for each PRx-group with patients above and below the CPP threshold, and the probabilities of achieving a favorable outcome calculated with Fisher's exact test. These calculations were done separately for the diffuse and focal groups.

A p value less than 0.05 was considered statistically significant.

Results

CPP, PRx, and Outcome

In the patient group as a whole, there was a highly significant difference in PRx between patients with favorable and unfavorable outcome. Patients with unfavorable outcome had higher values; i.e., patients with worse autoregulation were less likely to achieve a favorable outcome. In the combined group no relationship between CPP and outcome was observed (Table 3).

The relationship between PRx and outcome was essentially the same in the diffuse and focal subgroups, i.e., higher PRx (worse autoregulation) in patients with unfavorable outcome, although the result did not reach statistical significance in the focal case ($p = 0.06$). In diffuse injury patients there was no relationship between mean CPP and outcome, but in the focal group CPP was significantly higher in patients with unfavorable outcome (Table 3).

CPP and PRx, Combined Impact on Outcome

In the diffuse group, patients with PRx >0.1, i.e., disturbed autoregulation, CPP >70 was associated with a higher proportion of favorable outcome. No difference in proportions of favorable outcome was found in the other PRx-groups, when divided by CPP-level (Table 4). In the focal group, there were no differences in the proportions of favorable outcome in the three PRx-groups when divided by CPP-level (Table 5).

Table 3 CPP and PRx differences between patients with favorable and unfavorable outcome

Group	Outcome	Variable			
		CPP Median (IQR)	*p*	PRx Median (IQR)	*p*
All patients	Favorable	74.7 (70.3–77.8)	0.33	0.00 (−0.11–0.07)	0.002
	Unfavorable	77.2 (68.9–81.2)		0.08 (0.00–0.22)	
Diffuse	Favorable	75.9 (70.7–78.9)	0.22	−0.01 (−0.11–0.06)	0.04
	Unfavorable	71.9 (67.7–79.8)		0.05 (−0.01–0.18)	
Focal	Favorable	73.1 (67.9–77.1)	0.02	0.01 (−0.06–0.11)	0.06
	Unfavorable	78.7 (74.8–85.5)		0.10 (0.03–0.2)	

Diffuse injury group Marshall CT classes D1, D2, and D3; *Focal injury group* Marshall CT classes D4, EML, and NEML

CPP cerebral perfusion pressure, *PRx* pressure reactivity index, *IQR* interquartile range

Table 4 Diffuse injury group

	CPP	Unfavorable (GOSE 1–4)	Favorable (GOSE 5–8)	*p*
PRx <0.05	<70	4	8	0.23
	>70	5	27	
PRx >0.05, <0.1	<70	0	1	1.0
	>70	2	8	
PRx >0.1	<70	5	0	0.03
	>70	2	5	

Outcome by combination of CPP level and status of pressure reactivity. Marshall CT classes D1, D2, and D3

CPP cerebral perfusion pressure, *GOSE* extended Glasgow outcome scale

Table 5 Focal injury group

	CPP	Unfavorable (GOSE 1–4)	Favorable (GOSE 5–8)	*p*
PRx <0.05	<70	0	3	0.52
	>70	5	10	
PRx >0.05, <0.1	<70	1	1	1.0
	>70	4	2	
PRx >0.1	<70	1	2	0.54
	>70	7	4	

Outcome by combination of CPP level and status of pressure reactivity. Marshall CT classes D4, EML, and NEML

CPP cerebral perfusion pressure, *GOSE* extended Glasgow outcome scale

Discussion

General Considerations

Information on the status of cerebral autoregulation is considered important to take into account in the management of severely injured TBI patients [5]. Despite several methods of assessing cerebral autoregulation [2, 7, 10, 15–18], reliable real-time information remains elusive, and to date none of these methods is widely used in clinical routine.

The best available measure for continuous assessment of autoregulation status is the PRx, which is a measure of cerebral pressure autoregulation that has been shown to correlate closely with outcome in retrospective studies. High values of PRx (disturbed autoregulation) are strongly associated with unfavorable outcome or death [7, 19]. In previous work on PRx, many different subtypes of traumatic brain injury have been included in the studied patient populations. In the present work, we sought to examine the impact of pressure reactivity and CPP in different injury subtypes. The aim was to investigate whether the association between PRx and outcome is true in all injury subtypes; and whether different levels of CPP have different impact on outcome in different types of injury.

PRx and Outcome

In the present work, the expected relationship between PRx and outcome was found when considering the patient group as a whole; patients with an unfavorable outcome had higher PRx (more disturbed pressure reactivity). The same result was found, when the patients were divided according to Marshall CT class. The relationship was significant in the diffuse group, comprised of patients in Marshall class D1, D2, and D3 ($p = 0.04$), but not in the focal group (Marshall class D4, EML, and NEML) ($p = 0.06$).

In previous work by our group, using another methodology for assessment of pressure reactivity (slope of the regression line between ICP/ABP), impaired pressure reactivity was found to be a positive prognostic factor in surviving TBI patients treated according to an ICP-based protocol [4, 20]. The present study, using the same management protocol, was not able to replicate this finding

using PRx. Possibly the methodologies represent different aspects of pressure autoregulation. There is also the possibility that the patients differ, which may be one explanation for the different results if it is true that the type of injury influences the results as indicated by the present study. This finding deserves further study.

CPP and Outcome

In the focal group, high CPP was associated with worse outcome. One explanation may be the status of the blood–brain barrier (BBB). In case of disruption of the BBB integrity, there is an increased risk of capillary leakage and subsequent brain edema. In this case, a high CPP may be harmful even in case of relatively preserved autoregulation. This is the theory behind the Lund concept of TBI management, which aims at counteracting transcapillary filtration to avoid edema formation [21].

Brain edema after TBI can be of cytotoxic or vasogenic origin. Although the dominant mechanism is believed to be cytotoxic [22], the two types of edema may coexist [23]. Recent animal studies using dynamic contrast-enhanced MRI have studied BBB integrity after TBI, revealing more capillary leakage in more severe injury [24]. Another animal study targeting focal injury found more disrupted BBB and larger extent of perilesional vasogenic edema when lesion volume was larger [25]. Chieregato et al. [26] used xenon-CT to study the tissue surrounding traumatic contusions and traumatic hematomas in TBI patients. The results suggest a difference in pathophysiology of the perilesional tissue, where pericontusional edema formation in traumatic hematomas is primarily due to vasogenic mechanisms generated by the presence of the hemorrhagic core. The possibility of a difference in pathophysiology between diffuse and focal injuries in this respect should be further investigated.

Hyperemia, as defined by elevated CBF has been shown to occur in TBI, with peak incidence approximately day 1–3 after injury [27]. Hyperemia can be a global or regional phenomenon, and has been associated with both favorable and unfavorable outcome [28, 29]. The mechanism may be a drop in distal cerebrovascular resistance [27] and/or generation of vasoactive metabolites such as lactic acid, neuropeptides, and adenosine, as has been observed in "luxury perfusion" following ischemia [30, 31]. In case of intact pressure autoregulation, a small elevation in CBF may represent an appropriate coupling between CBF and increased metabolism and be a positive prognostic factor [32, 33]. In case of severe injury and gross dysfunction of pressure autoregulation hyperemia may be a malignant condition, associated with intracranial hypertension and unfavorable outcome [34].

Chieregato et al. [35] found prolonged hyperemia in the cortex underlying an evacuated subdural hematoma in patients with unfavorable outcome. This mechanism may also be a part of the explanation why higher CPP levels were associated with unfavorable outcome in diffuse injury patients, as capillary leakage and edema formation may be worsened in case of increased tension in an already dilated vascular bed. Vascular engorgement may also increase risk of intracranial hypertension with higher CPP values, when cerebrospinal compliance is exhausted.

As we did not measure CBF in this study, the impact of hyperemia in our patients is unclear. The interplay of CPP, CBF, and cerebral autoregulation deserves further study.

PRx, CPP, and Outcome

When adjusting the focal group patients according to status of pressure autoregulation, the level of CPP was not associated with outcome. It should be noted, however, that the numbers of patients in these subgroups were small (Table 5).

In the diffuse group, CPP values above 70 mmHg were associated with a favorable outcome in patients with disturbed autoregulation (PRx >0.1). This association was not found in patients with preserved or moderately deranged autoregulation, suggesting that in patients with diffuse injury and highly deranged pressure autoregulation, a moderately higher CPP may be beneficial. The risk of edema formation may be lower because of less injured BBB, as discussed above, and, therefore, these patients, with impaired autoregulation of CBF, may be helped by a moderately higher CPP to establish an adequate CBF. The actual level of CPP that is most beneficial is not clearly established in this investigation. However, the values that seemed beneficial were not exceedingly high; the median/IQR CPP for diffuse injury patients with favorable outcome was 75.9 (70.7–78.9) mmHg. The possibility of this patient subpopulation (diffuse injury and impaired pressure autoregulation) being helped by a small artificial increase in CPP should be further investigated.

As discussed above, numerous previous studies have indicated that the management of CPP should be guided by pressure autoregulation status. The details of the desired autoregulation-based management strategy, however, are still unclear [36]. In the present work it was found that for patients with "focal" injuries elevated CPP was associated with worse outcome, consistent with previous studies from our center [20, 37]. A new finding of the current study is that patients with diffuse injuries and failed autoregulation manifest a different pattern; in this case elevated CPP was found to be associated with better outcome. This may prove to be an important clue for clinical applications.

Conclusion

Our results give rise to the hypothesis that TBI patients with diffuse injury differ from those with mass lesions. In the latter higher levels of CPP may be harmful, possibly due to BBB disruption. In the group with diffuse injury, higher levels of CPP may be beneficial in patients with disturbed pressure autoregulation. These hypotheses should be tested with further studies.

Conflict of interest Ulf Johnson, Anders Lewén, Elisabeth Ronne-Engström, Tim Howells and Per Enblad declare that they have no conflict of interest.

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