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ORIGINAL ARTICLE - BRAIN INJURY

Time spent with impaired autoregulation is linked with outcome in severe infant/paediatric traumatic brain injury

Konstantin Hockel[1] · **Jennifer Diedler**[1] · **Felix Neunhoeffer**[2] · **Ellen Heimberg**[2] · **Carmen Nagel**[3] · **Martin U. Schuhmann**[1]

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Abstract
Background It could be shown in traumatic brain injury (TBI) in adults that the functional status of cerebrovascular autoregulation (AR), determined by the pressure reactivity index (PRx), correlates to and even predicts outcome. We investigated PRx, cerebral perfusion pressure (CPP) and intracranial pressure (ICP) and their correlation to outcome in severe infant and paediatric TBI.
Methods Seventeen patients (range, 1 day to 14 years) with severe TBI (median GCS at presentation, 4) underwent long-term computerised ICP and mean arterial pressure (MAP) monitoring using dedicated software to determine CPP and PRx and optimal CPP (CPP level where PRx shows best autoregulation) continuously. Outcome was determined at discharge and at follow-up using the Glasgow Outcome Scale.
Results Favourable outcome was reached in eight patients, unfavourable outcome in seven patients. Two patients died. Nine patients underwent decompressive craniectomy to control ICP during Intensive Care Unit treatment. When dichotomised to outcome, no significant difference was found for overall ICP, CPP and PRx. The time with severely impaired AR (PRx >0.2) was significantly longer for patients with unfavourable outcome (64 h vs 6 h, $p = 0.001$). Continuously impaired AR of ≥24 h and age <1 year was associated to unfavourable outcome. Children with favourable outcome spent the entire monitoring time at or above the optimal CPP.
Conclusions Integrity of AR has a similar role for outcome after TBI in the paediatric population as in adults. The amount of time spent with deranged AR seems to be associated with outcome; a factor especially critical for infant patients. The results of this preliminary study need to be validated in the future.

Keywords Paediatric · Traumatic brain injury · Outcome · Cerebral autoregulation · Pressure reactivity · PRx

Abbreviations

AR	cerebrovascular autoregulation
CPP	cerebral perfusion pressure
DC	decompressive craniotomy
ICP	intracranial pressure
MAP	mean arterial pressure
PRx	pressure reactivity index
TBI	traumatic brain injury

Introduction

Traumatic brain injury (TBI) remains the leading cause for morbidity and mortality in children, despite the fact that moderate and severe forms account for only 10% of all TBIs [14].

Cerebral hypoperfusion, which eventually leads to secondary brain damage, is a well-described phenomenon in children and an assumed leading cause for unfavourable outcome after TBI in children [20, 27]. It can occur despite "normal" intracranial pressures. The maintenance of a sufficient cerebral

✉ Konstantin Hockel
Konstantin.hockel@med.uni-tuebingen.de

[1] Section of Paediatric Neurosurgery, Department of Neurosurgery, University Hospital of Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

[2] Paediatric Intensive Care Medicine, University Children's Hospital of Tübingen, Tübingen, Germany

[3] Department of Paediatric Surgery, University Children's Hospital of Tübingen, Tübingen, Germany

Table 1 Patient characteristics

No.	Sex (f/m)	Age (months)	Initial GCS	Mechanism of injury	Initial CT findings	Surgical intervention	Time of surgery (days)	GOS at D/C	GOS at F/U
1	m	8	3	cupboard hit on head	ASDH, ICH left	DC bilat.	0	I	-
2	m	179	6	MVC	ICH left	DC left, HEvac.	2, 6	III	III
3	f	38	7	fall 4 m	EDH left	HEvac.	0	IV	V
4	m	<1	3	forceps delivery	ASDH, hypoxia	DC right	2	III	III
5	m	156	3	MVC	ASDH right	DC right	0	I	-
6	f	28	5	horse acc.	cont. Bilat.	DC bilat.	0, 6	II	III
7	m	39	7	fall 5 m	cont., EDH right	HEvac.	0	IV	V
8	m	147	-	fall 4 m	ASDH, cont. Bilat.	DC bilat.	5	IV	V
9	m	<1	3	MVC	EDH, ASDH left	DC left, HEvac.	0	II	-
10	m	125	6	skateboard acc.	EDH, ASDH left	HEvac.	0	V	V
11	f	28	4	fall 2 m	ASDH bilat.	-	-	IV	-
12	f	12	4	fall 10 m	ASDH right	-	-	III	IV
13	m	47	3	MVC	DAI, oedema	DC bilat.	5	V	V
14	m	122	6	MVC	SAH	-	-	V	V
15	m	4	3	battered child	ASDH bilat., SVT	-	-	II	III
16	m	7	7	unknown	ASDH right	DC right, HEvac.	0, 3	II	III
17	m	137	10	fall 3 m	ASDH, cont. Right	DC bilat, HEvac	0, 2	II	-

MVC motor vehicle accident, *ASDH* acute subdural haematoma, *EDH* epidural haematoma, *DAI* diffuse axonal injury, *bilat.* bilateral, *cont.* contusion, *DC* decompressive craniectomy, *HEvac* haematoma evacuation, *D/C* discharge, *F/U* follow-up

perfusion pressure (CPP) by adjusting arterial blood pressure plays a crucial role apart from treatment of raised intracranial pressure (ICP) both by conservative means and surgical intervention. Paediatric guidelines regarding CPP management, however, define a relatively wide range of critical thresholds, between 40 and 65 mmHg as target, with the need for age-dependent adjustments [15].

In order to be able to manage CPP individually, online bedside information about the brain's intrinsic capacity of regulating vessel resistance to maintain a stable cerebral blood flow, i.e. cerebrovascular autoregulation (AR), is necessary [5]. A continuous method of assessing AR by using a correlation index between ICP and arterial blood pressure (ABP) has been implemented for adult Intensive Care Unit (ICU) care of TBI patients for many years [11]. This pressure reactivity index as a measure of AR (PRx) has been shown to predict the development of unfavourable outcome and allows analysis of cerebral perfusion pressure thresholds to optimise the autoregulatory function [3, 11, 24]. Previous studies were able to demonstrate that the concept of PRx monitoring is transferable to the paediatric population [4, 16, 19, 29].

Our goal in this series of severe infant and paediatric TBI was to demonstrate that independent of age continuous assessment of cerebral autoregulatory capacity is feasible. Furthermore, we investigated the correlation of patient outcome to the status of AR, which has been shown to exist in adults. In addition, emphasis was put on the temporal profile of CPP levels and its association to AR. The correlation of AR status and CPP treatment range was analysed for three different age groups, i.e. infant (<1 year), children at the age between 1 and 4 years, and older children (>4 years).

Patients and methods

Patient inclusion and general management

Seventeen consecutive patients with severe traumatic brain injury were included in this retrospective analysis after being admitted to the paediatric ICU between January 2009 and May 2014. In our institution, all patients with brain injury requiring intubation and sedation are receiving ICP monitoring and computerised monitoring as described below. Data were retrospectively analysed with institutional review board approval (367/2016BO2). The local ethics committee granted waiver of patient consent. General patient characteristics are summarised in Table 1.

As all patients had suffered severe TBI, intubation, mechanical ventilation and analgosedation was initiated immediately on scene in the pre-hospital phase. When initial computed tomography (CT) imaging revealed brain trauma sequelae needing immediate surgical intervention, intraparenchymal ICP monitoring was installed intraoperatively. Otherwise ICP probes were implanted at the paediatric ICU and computerised monitoring implemented immediately thereafter. Sixteen patients were primary admissions; one was a

secondary referral for further ICU treatment on day 6, soon after bilateral small decompressive craniectomy had been performed elsewhere.

Intensive care management was conducted according to our current paediatric neurointensive care standards and according to current paediatric TBI guidelines [15]. Sedation was maintained with midazolam and fentanyl. Mechanical ventilation was adjusted to keep arterial pO_2 at 100 ± 10 mmHg and arterial pCO_2 between 35 and 38 mmHg. Vasopressors (noradrenalin, dopamine, vasopressin) were titrated in cases of arterial hypotension despite normovolemia according to the general age-based guidelines. Haemoglobin levels were kept between 9.5 and 10 g/l. In cases of intracranial hypertension refractory to all conservative treatment options according to guidelines, decompressive craniectomy (DC) or removal of secondary epidural or subdural haematoma was chosen as primary second tier treatment option.

Neurological status and Glasgow Outcome Scale (GOS) was assessed in all surviving patients before discharge and at follow up 6 months after trauma (12 patients) and dichotomised into favourable outcome (GOS 4–5) and unfavourable outcome (GOS 2–3). Two patients with early fatal outcome (case 1 and case 4, GOS 1; *see* Table 1), which suffered an initial severe ischaemic brain damage and developed immediately uncontrollable high ICP and low CPP despite initial DC, were excluded from outcome-related analysis (reasons given below). Three patients were lost for follow up examination. Here discharge status was used for further analysis.

Neuromonitoring, assessment of cerebral autoregulation and CPP management

A Neurovent-P probe (Raumedic, Helmbrechts, Germany), for assessment of intraparenchymal ICP, was inserted into the frontal white matter via a one-lumen bolt or directly during intraoperative dural opening. If feasible, the probe was placed within the more severely injured hemisphere (12/17 patients). Mean arterial pressure (MAP) was continuously monitored by a catheter inserted into the radial artery with the transducer referenced to the foramen of Monro. ICP and MAP signals were continuously recorded as analogue signals on a bedside-mounted device (Datalogger MPR; Raumedic) and transferred to the hospital monitoring system. Monitoring parameters were in addition digitally sampled at a rate of 100 Hz by a bedside notebook running ICM+ software (Cambridge Enterprise, Cambridge, UK) over the whole observation time. The ICM+ software was used for both online display of data and retrospective analysis of recorded monitoring parameters.

CPP was calculated as the difference between MAP and ICP. Pressure reactivity index (PRx) represents a correlation analysis of spontaneous slow waves of the MAP and ICP signal providing information about the vasoreactivity or pressure reactivity of the cerebral vasculature, which is a key component of cerebrovascular autoregulation. PRx was calculated as moving Pearson correlation coefficient between averaged (10-s periods) ICP and MAP calculated over a 5-min moving window as described previously [11]. Possible values therefore range from −1 to 1. Negative or zero values indicate intact pressure reactivity, i.e. increase in MAP results in cerebral vasoconstriction with decrease in ICP (negative correlation); positive values, when vessels passively dilate to increase in MAP (positive correlation), indicate disturbed pressure reactivity [10].

In all patients, the bedside notebook continuously displayed neuromonitoring parameters (MAP, ICP, CPP, PRx) updated every minute. ICU personnel had access to the neuromonitoring data, in particular to the status of AR and correlation of PRx and CPP over a variable 4– to 10-h window giving information on a potentially optimal CPP (CPPopt) where vasoreactivity and AR is best as described previously [3, 25]. CPPopt is defined as the CPP where PRx reaches its minimum value when plotted against CPP (on a typically U-shaped CPPopt curve). CPP was targeted in principal according to guideline-based standards (CPP >40 in infants with a sliding increase to >60 mmHg in >15 years) [15]. However, adjustment of CPP to CPPopt of the last 12 h, re-assessed twice a day, was encouraged and a general policy—if ABP levels did not exceed age matched upper limits—but not mandatory according to a strict protocol.

Data analysis and statistics

For retrospective analysis ICP and MAP data were subjected to manual artefact detection (based on the MAP curve, e.g. due to arterial blood gas sampling) and removal. In the final analysis of physiological variables, i.e. ICP, MAP, CPP and PRx, mean values were calculated for the entire treatment period. Mean overall ICP, CPP and PRx values were compared to outcome. For all detailed analyses of ICP, CPP and PRx, and their relationship to outcome (favourable vs unfavourable), we excluded the two patients with early fatal outcome. The overall monitoring period was segmented into 1-h intervals for each patient. For each 1-h interval, mean ICP, CPP and PRx values were calculated. The PRx values were sorted according to the mean CPP of the respective sampling interval, by using 5-mmHg bins. The sorted PRx values were averaged for each CPP bin in every patient, resulting in a CPPopt curve (*see* above) for the entire monitoring period. Each of the 15 PRx/CPP plots was then dichotomised for favourable and unfavourable outcome group and for three different age groups (Group A <1 year, Group B between 1 and 4 years, Group C >4 years). Mean values of PRx were calculated for each CPP bin as mean of means for the entire cohort.

Table 2 Outcome characteristics

Outcome group	Favourable outcome	Unfavourable outcome
GOS (median, range)	5 (4–5)	3 (2–3)
Age (months, mean/range)	70 (12–147)	51 (1–179)
GCS (median/range)	5 (3–7)	5 (3–10)
DC (no. of patients)	1	6
ICP (mmHg; mean ± SD)	12.7 ± 3.8	11.8 ± 3.6
CPP (mmHg; mean ± SD)	61.1 ± 5.1	57.8 ± 9.5
PRx (a.u.; mean ± SD)	-0.10 ± 0.16	-0.03 ± 0.16
ICP >20 mmHg (time %)	10.1 ± 1.6	10.1 ± 2.5
PRx >0.2 (time %)	7.7 ± 1.7	20.5 ± 2.3 ($p = 0.06$)

GOS Glasgow Outcome Scale, *GCS* Glasgow Coma Scale, *DC* decompressive craniectomy

Following similar thresholds in the literature, a PRx above 0.2 was defined as impaired cerebrovascular reactivity, whereas PRx below 0 marked clearly intact autoregulation [11, 24]. For each patient, the time spent with a PRx above 0.2, between 0 and 0.2, and below 0 was evaluated as absolute time (hours) and calculated as the percentage of the total monitoring time. The respective time and percentage values were then dichotomised for favourable and unfavourable outcome groups. Regarding ICP thresholds, we assumed critically elevated ICP above 20 mmHg and normal ICP below 15 mmHg. Consecutively, the percentage of monitoring time with ICP above 20, between 15 and 20, and below 15 mmHg was calculated and dichotomised for favourable and unfavourable outcome groups.

ICP, CPP and PRx values were compared between favourable and unfavourable outcomes with the Mann-Whitney *U* test (SigmaStat 12.5, Germany). Correlation analysis between PRx, ICP and outcome was performed via Pearson correlation. Statistical significance was assumed for $p < 0.05$ if not indicated otherwise.

Results

Clinical data and outcome

The age distribution varied between 1 day and 14 years, with 6/17 patients in the age group A (below 1 year), 5/17 patients in group B (between 1 and 4 years) and 6/17 patients in group C (4 years and older). The mechanism of head injury included mainly falls from significant height, motor vehicle and sports accidents. Trauma CT scans showed epidural haematoma in 25%, acute subdural haematoma in 60%, intracerebral haemorrhage in 10% and significant brain contusions in 40% of the cases. In 3 of 17 patients, clinical and radiographic signs of tentorial herniation were present on admission. Nine of 17 patients underwent immediate surgery (haematoma evacuation ± DC), and a further four patients within the next days (Table 1).

Two patients died early due to uncontrollable intracranial hypertension from the very beginning, with mean ICP of 57 and 80 mmHg, CPP values below 20 mmHg and completely lost AR (mean PRx close to 1), indicating profound cerebral ischaemia already at the time of admission to the ICU. Therefore these patients were excluded from further detailed analysis.

Of the remaining 15 patients, eight experienced a favourable outcome—GOS 4 and 5—and seven an unfavourable outcome—GOS 2 and 3 (Table 1). The favourable and unfavourable outcome groups had comparably low median initial GCS of 5 (range, 3–7) and 5 (range, 3–10), respectively, but differed in the rate of DC, with 1/8 and 6/7 patients for the respective groups. Mean age in the two outcome groups was 5.9 and 4.2 years for favourable and unfavourable outcome, respectively (*see* Table 2).

The patients were equally distributed to the age groups A (<1 year), B (1–4 years) and C (>4 years) with $n = 5$ per group. Outcome was more favourable with increasing age, with a median GOS of 3, 4 and 5 for the groups A, B and C, respectively.

ICP, CPP and cerebral autoregulation (AR)

A total of 2,999 h of monitoring data was evaluated, with a mean of 152 h per patient (range, 22–355 h). The mean duration of monitoring was 153.8 h and 191.1 h in favourable and unfavourable outcome group, respectively.

No difference, not even a trend, was found between mean ICP and CPP values ($p > 0.05$) between the favourable (ICP, 12.7 ± 3.8 mmHg; CPP, 61.1 ± 5.1 mmHg) and unfavourable (ICP, 11.8 ± 3.6 mmHg; CPP, 57.8 ± 9.5 mmHg) outcome groups. ICP was identical in both outcome groups when separated into three different groups: normal (<15 mmHg), critical (between 15 and 20 mmHg) and elevated (>20 mmHg) (Fig. 1).

In all 15 patients, independent of age, assessment of AR by PRx was feasible during monitoring time. The majority of the patients (n = 12/15) had mean total PRx values around or

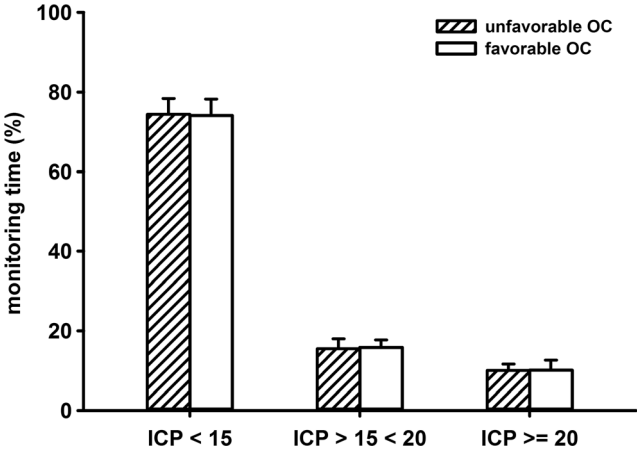


Fig. 1 ICP dichotomised according to outcome and categorised into critical (ICP >20 mmHg), elevated ICP (ICP, 15–20 mmHg) and normal ICP (ICP <15 mmHg). Relative fraction of the three ICP categories displayed as percentage of total monitoring time (*y*-axis) for the unfavourable outcome (diagonal pattern, $n = 7$) and favourable outcome ($n = 8$) groups

below zero, suggesting intact AR for the majority of their monitoring time. After dichotomising according to outcome, mean PRx exhibited a trend for higher PRx values (more disturbed AR) in the unfavourable outcome group, -0.03 ± 0.16 versus -0.10 ± 0.16, $p > 0.05$.

Detailed PRx and CPP analysis

When plotting mean PRx against the CPP range (in 5 mmHg bins) a continuously intact AR (mean PRx <0) was observed for the entire CPP range (50–80 mmHg) in the favourable outcome group (Fig. 2a). In the unfavourable outcome group, CPP values below 60 mmHg were associated with increasing PRx, thus disturbed AR (Fig. 2b). Approximately 50% of the monitoring time was spent at a PRx above 0 and a CPP below 60 mmHg in this group.

The assessment of the temporal profile of mean PRx by 1-h intervals stratified according to the three different AR categories (PRx <0, PRx = 0–0.2, PRx >0.2) displayed differences between the outcome groups. In the unfavourable outcome group, a greater proportion of monitoring time was spent with an impaired AR (PRx >0.2; $20.5 \pm 2.3\%$ versus $7.7 \pm 1.7\%$, $p = 0.06$), which resulted in a significantly higher duration of impaired AR of 64 h versus 6 h in the favourable outcome group ($p < 0.01$, Fig. 2c). A continuously disturbed AR (PRx >0.2) for more than 24 h was related to unfavourable outcome in 100% of the cases (five patients).

CPP values ranged between approximately 30 to 80 mmHg for age group A (<1 year), 40 to 80 mmHg for group B (1–4 years) and 50 to 80 mmHg for group C (>4 years) (*see* Fig. 3a-c). All age groups had predominantly functional AR with negative PRx values at higher CPP values, accounting for 57%, 95% and 92% of the monitoring time in the groups A, B and C, respectively. In the infants of group A, however, only a narrow corridor of between 55 and 65 mmHg existed, where AR was fully functional with negative PRx. In 33% of the monitoring time, CPP was below 55 mmHg with an increasingly impaired AR (PRx >0), which was also found at a high CPP above 65 mmHg accounting for 10% of the time.

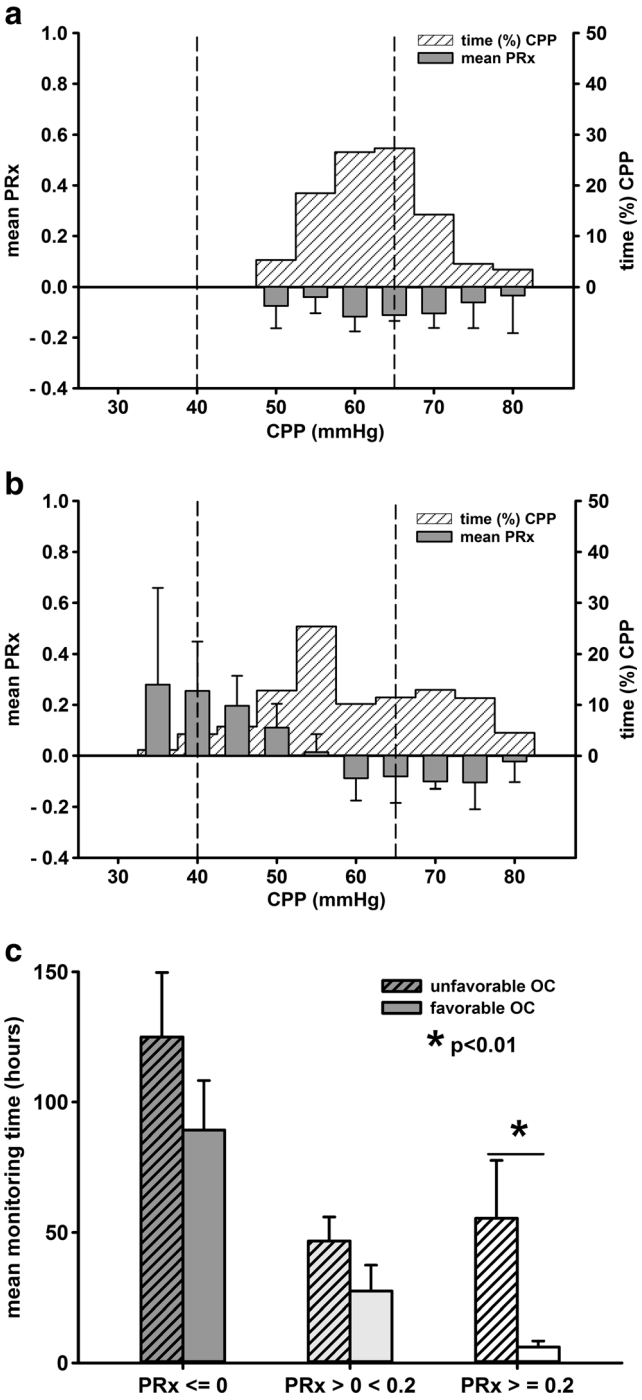
Discussion

In paediatric TBI patients, spontaneous alterations of cerebral haemodynamics from hypoperfusion to hyperaemia are present [2, 6, 9, 23]. Apart from keeping ICP in a possibly harmless range, the aim of CPP management is to avoid the extremes, where high arterial pressure on the vascular bed may result in cerebral oedema or swelling and insufficient perfusion pressures lead to cerebral hypoperfusion and ischaemia [5].

Even if intracranial hypertension is successfully treated, recent data show that, despite good ICP control, up to 50% of the children nevertheless exhibit an unfavourable outcome following TBI [17]. Excluding the two patients who died of early malignant brain oedema and continuous intractable intracranial hypertension within 48 h, mean ICP values in all others were below the intended threshold of 20 mmHg and even below 15 mmHg in approximately 74% of monitoring time. The percentage of monitoring time with critical episodes of raised ICP, i.e. ICP above 20 mmHg, was equally distributed. Outcome, however, was classified unfavourable in seven patients of the remaining cohort, which on the one hand reflects the severity of TBI in these cases with median initial GCS 5, but on the other hand also supports the thesis that pure ICP threshold-guided management does not offer sufficient protection alone.

Regarding the following discussion of CPP and autoregulation in paediatric TBI patients, one must keep in mind the major limitations of this study, which are its small sample size, its mono-centre character and its retrospective nature, so the conclusions must be drawn with caution and therefore can only be considered preliminary.

The disturbance of AR in adult TBI patients is meanwhile a well-described phenomenon [11, 24]. Recent data show that impairment of AR is an independent and serious risk factor for worse outcome [7]. There are only limited data in infants and newborn regarding the existence of AR and its usability for monitoring. Brady and co-workers, using Doppler based AR monitoring in premature babies, could recently show that cerebral blood flow AR is present between the 23rd and 29th week of gestation [21]. Applying different techniques of assessment, several groups have investigated AR capacity in children and the role of AR following TBI [4, 12, 16, 18, 19, 22, 28, 29]. In the majority of studies a loss or at least significant impairment of AR could be found in the initial



◀ **Fig. 2** **a** Mean values of PRx in the favourable outcome (*grey bars*, $n = 8$) group plotted against CPP categorised in 5-mmHg bins (*left y*-axis). Relative fraction (%) of the overall monitoring time for each respective CPP bin (5 mmHg) (*right y*-axis). *Dotted vertical lines* at CPP 40 and 65 mmHg indicate guideline thresholds. **b** Mean values of PRx in the unfavourable outcome (*grey bars*, $n = 7$) group plotted against CPP categorised in 5-mmHg bins (*left y*-axis). Relative fraction (%) of the overall monitoring time for each respective CPP bin (5 mmHg) (*right y*-axis). *Dotted vertical lines* at CPP 40 and 65 mmHg indicate guideline thresholds. **c** PRx dichotomised into intact AR (PRx <0, *dark grey bars*), disturbed AR (PRx >0.2, *white bars*) and "grey zone" AR (PRx >0 but <0.2, *grey bars*). The *y*-axis shows the three AR categories displayed as absolute value (hours) between the unfavourable outcome (diagonal pattern, $n = 7$) and favourable outcome ($n = 8$) groups (*$p < 0.01$ by Mann-Whitney *U* test)

phase [4, 16, 19, 22, 28, 29]. Moreover this impairment of AR was in most cases associated with unfavourable outcome, i.e. lower survival rate. The method of assessing AR by continuously quantifying pressure reactivity (PRx) has clear advantages over discontinuous assessments [4, 16]. Cerebrovascular reactivity of the precapillary resistance vessels, which is a dynamic phenomenon, has to be assumed to be not static but changing during the course of time and treatment on the ICU [26]. Thus it should be accessible to the treating team continuously by a software solution that allows bedside display and review with variable retrospective windows.

This concept is corroborated by the presented data. Firstly, we show that continuous AR monitoring by PRx is feasible independent of age, even in the first days of life. After severe TBI in infants/children, disturbance of AR by alterations of PRx can be quantified.

In contrast to the most recently published data on PRx in paediatric TBI [16, 29], we do not see any correlation between outcome and initial GCS, ICP or CPP in this cohort. As already seen in a pilot study [19] with preliminary data, mean PRx of the total monitoring time and the percentage of disturbed AR did not show significant difference between the outcome groups (excluding the two early non-survivors). Now we can demonstrate, however, that the absolute amount of time with lost AR in the first critical days after TBI, i.e. days 1–5, in one case up to day 7, seems to be associated with unfavourable outcome, since we showed a significantly longer "time load" = dose of deranged autoregulation in this group. Even though vasoreactivity may return and PRx decreases to more normal (negative) values in the course of time and ICU treatment, initially absent autoregulation of cerebral blood flow may have caused sufficient additional damage. The thresholds of PRx for evaluating AR status and its correlation to outcome still have to be defined more precisely in children, possibly also age related. In adult TBI, a lower threshold of overall mean PRx for favourable outcome was defined at 0.05 and at 0.25 for survival, with a "grey zone" in between [24]. In our cohort, a continuously increased PRx above 0.2 for more than 24 h (hourly mean value) was associated with unfavourable outcome in 100% (five of seven patients in the unfavourable outcome group).

A continuous AR assessment allows correlation to the relative CPP values. A retrospective analysis in adult TBI has already demonstrated that CPP values in the proximity of intact AR is leading to a more favourable outcome [3, 25].

The relative distribution of CPP values in our cohorts (Figs. 2a, b and 3a-c) leads to the assumption that the

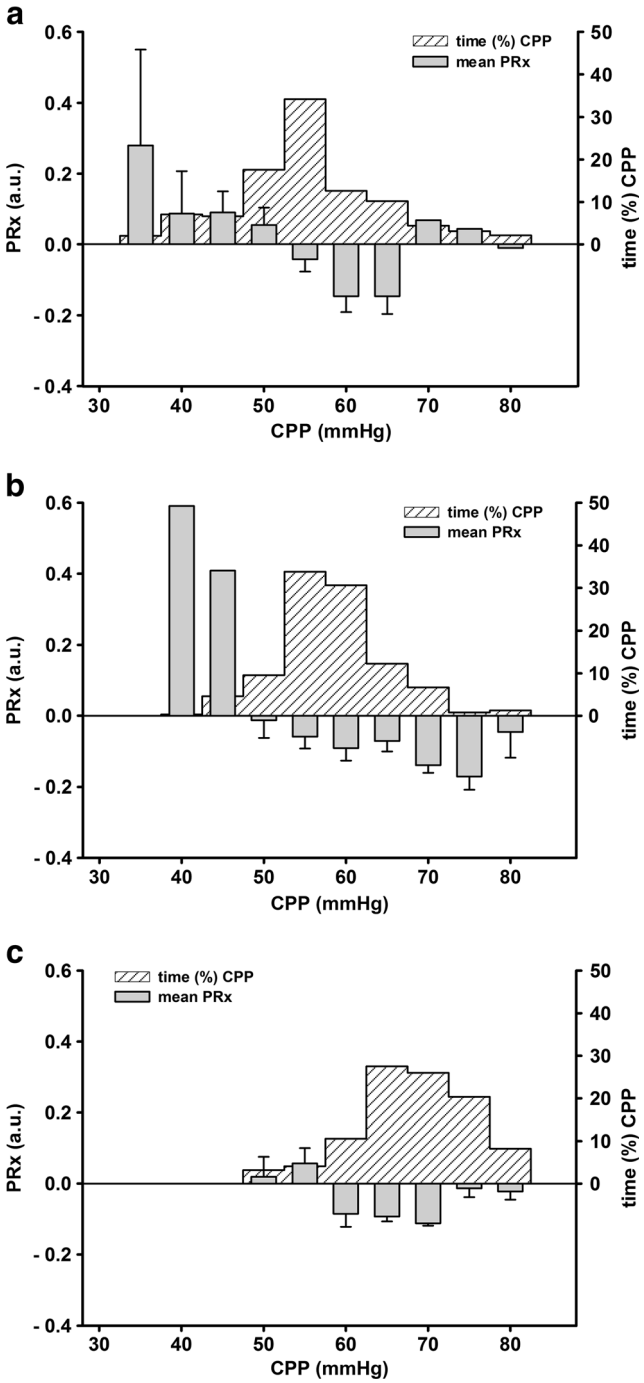


Fig. 3 Mean values of PRx in the age groups A (**a**, <1 year, $n = 5$), B (**b**, between 1 and 4 years, $n = 5$) and C (**c**, >4 years, $n = 5$) plotted against CPP categorised in 5 mmHg bins (*grey bars*, *left y*-axis). Relative fraction (%) of the overall monitoring time for each respective CPP bin (5 mmHg) (*right y*-axis)

bedside online display of PRx values and its correlation to CPP (CPPopt curve) may have affected CPP management. CPPopt-guided therapy implies managing CPP to a target value where AR is best, i.e. PRx is lowest, over the past hours of monitoring [25]. Both in the favourable/unfavourable outcome analysis and among the different age groups CPP values have been (temporarily) employed that are clearly higher than "generally assumed" age-related thresholds, e.g. CPP 40–65 mmHg, although knowledge about those age-related thresholds is still scarce [8, 15]. In the favourable outcome group, a functioning AR (PRx <0) was shown over the entire CPP range (50-80 mmHg). Which means, in turn, that we might have succeeded for the majority of time to steer the patients successfully into a CPP range with intact autoregulation, despite a regulation protocol just by making PRx visible and conveniently accessible. In the unfavourable outcome group, on the contrary, in about 50% of the time PRx was indicating a progressively deteriorating autoregulatory capacity as CPP decreased below 55-60 mmHg. Therefore it can be hypothesised for this unfavourable outcome group that despite the knowledge of a suboptimal CPP either it was not consistently feasible to raise CPP to the target area or that the inability to regain a functioning AR despite CPP elevation indicates a prognostically unfavourable significance of the underlying brain damage.

Regarding the elevation of CPP by ABP manipulations, it has to be kept in mind that increasing the CPP above the CPPopt level has no additional beneficial effect on cerebral perfusion but might rather increase the risk for hyperaemia, vasogenic oedema and unfavourable outcome [3, 13].

For our TBI cohort, this reveals two critical aspects. In the favourable outcome group and age group C (>4 years) CPP ranges were employed for some time that were not only beyond TBI guidelines but also above a likely CPPopt level. Thus, despite the fact that an area of intact AR had been reached, a certain amount of overtreatment regarding CPP elevation occurred with potentially negative effects. Fortunately the outcome does not reflect possible negative side effects of CPP over-treatment. Secondly, in patients in whom AR is partially or temporarily disturbed, especially in infants (age group A, Fig. 3a), only a narrow corridor of CPP values with preserved vasoreactivity might be found and these children might be easily over- or under-treated.

Our data also show that the influence of age in paediatric TBI remains important and critical. Previous data demonstrated a higher mortality and worse outcome in patients younger than 2 years [2] and an increase of the presumed optimal CPP with age in paediatric TBI [16]. We observed, as expected, an increasing CPP range with older age, but also a higher frequency of too low CPPs and smaller windows of intact AR. Interestingly, the lower cut-offs for CPP according to deteriorating PRx, with 40 mmHg for the infant group (Fig. 3a) and 50 mmHg for older children (Fig. 3b, c), resemble the values that have been associated with unfavourable outcome in the past, but were identified indirectly [1, 8, 17]. Whether the more favourable outcome for the older patient groups, i.e. groups B and C versus A,

is an expression of a less severe initial trauma or related to the ability of bringing CPP in a range of intact AR cannot be sufficiently evaluated from these data.

Conclusions

Cerebrovascular pressure reactivity and associated blood flow autoregulation is a fundamental property of life and essential for maintenance of adequate brain perfusion. Despite its limitations and preliminary character, the presented study indicates that in infants as well as in children, adult principals are valid and possibly even more important, i.e. that early loss of AR capacity after TBI may serve as an additional prognostic marker for unfavourable outcome and should be addressed actively. Whether PRx-guided CPP therapy to reach and then maintain optimal cerebral perfusion, between hypoperfusion (lower limit of autoregulation) and hyperaemia, does have a superior effect on patient outcome compared to standard treatment cannot be concluded from these preliminary data.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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Comments

This is another work showing that ICP is important but not the major factor. Similarly to the sun or the horizon we believed to be the centre of the world and flat, we were misled.ICP is the obvious visible factor but the essential factor is continuous adequate local perfusion and this is strongly regulated. The hypothesis is that preserved autoregulation and autoregulation buffers protect brain tissue from secondary hypoperfusion. The loss of autoregulation makes it a challenge and, if severe, impossible to keep the perfusion adequate at all times, resulting in successive insults progressively amplifying the initial injury. Autoregulation can be assessed by various tools but PRx seems to have advantages and is probably the most reported. CPPopt is a great concept that, like an index or a medication adjustment to the patient's weight, normalises the perfusion pressure to the specific conditions of each patient at a specific time. This work adds evidence to the concept of CPPopt driven TBI management and extends it to the paediatric population.It is time for the community to join efforts to rapidly assess formally in a massive multicentre trial the concept of CPPopt-driven management of TBI patients.

Philippe Bijlenga

Geneve, Switzerland