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ORIGINAL PAPER

Brain tissue oxygen tension monitoring in pediatric severe traumatic brain injury

Part 2: Relationship with clinical, physiological, and treatment factors

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Abstract
Introduction Brain tissue oxygen tension ($PbtO_2$) monitoring is used increasingly in adult severe traumatic brain injury (TBI) management. Several factors are known to influence $PbtO_2$ in adults, but the variables that affect $PbtO_2$ in pediatric TBI are not well described. This study examines the relationships between $PbtO_2$ and (1) physiological markers of potential secondary insults commonly used in pediatric TBI, in particular intracranial pressure (ICP), cerebral perfusion pressure (CPP), and systemic hypoxia, and (2) other clinical factors and treatment received that may influence $PbtO_2$.
Materials and methods In this prospective observational study, 52 children (mean age, 6.5±3.4 years; range, 9 months to 14 years old) with severe TBI and a median post-resuscitation Glasgow Coma Score (GCS) of 5 were managed with continuous $PbtO_2$ monitoring. The relationships between $PbtO_2$ parameters ($PbtO_{2_{low}}$, $PbtO_2<5$, $PbtO_2<10$, and $mPbtO_{2_{24}}$) and clinical, physiological, and treatment factors were explored using time-linked data and Spearman's correlation coefficients.
Results No clinical, physiological, or treatment variable was significantly associated with all $PbtO_2$ parameters, but individual associations were found with initial GCS ($PbtO_2<5$, $p=0.0113$), admission Pediatric Trauma Score ($PbtO_2<10$, 0.0175), mICP>20 ($mPbtO_{2_{24}}$, $p=0.0377$), CPP_{low} ($PbtO_{2_{low}}$, $p=0.0065$), CPP<40 ($PbtO_{2_{low}}$, $p=0.0269$; $PbtO_2<5$, $p=0.0212$), $P_aO_2<60$ ($mPbtO_{2_{24}}$, $p=0.0037$), $S_aO_2<90$ ($PbtO_{2_{low}}$, $p=0.0438$), and use of inotropes during ICU care ($PbtO_{2_{low}}$, $p=0.0276$; $PbtO_2<10$, $p=0.0277$; $p=mPbtO_{2_{24}}$).
Conclusion Delivery of oxygen to the brain is important to limit secondary neuronal injury after severe TBI. Our data show that $PbtO_2$ is poorly predicted by clinical and physiological factors commonly measured in the pediatric ICU. Multimodality monitoring may be needed to detect all secondary cerebral insults in pediatric TBI.

Keywords Brain oxygen · Children · Traumatic brain injury · Intracranial pressure · Cerebral perfusion pressure · Monitoring

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Introduction

Neuronal injury after severe traumatic brain injury (TBI) occurs through primary or secondary mechanisms. Primary injury is caused at the moment of injury, but apart from prevention, e.g., a seat belt, there is little specific treatment for it. Because secondary insults and in particular hypoxia, hypotension, and intracranial hypertension are leading factors associated with poor outcome, TBI management is focused on ways to improve oxygen delivery, reduce intracranial pressure (ICP), and maximize cerebral perfusion pressure (CPP) [2, 3, 7, 12, 25, 27, 28, 49, 50]. Although this approach has never been validated in a randomized clinical trial, it is believed to improve TBI outcome and represents a significant part of the "Guidelines for the Management of Severe Brain Injury" [6]. The evidence used to create the original "Guidelines," however, did not specifically address children. Recent publications have attempted to address this deficiency, and now, separate guidelines that describe the management of childhood TBI have been published [1]. As in the adult guidelines, these "Pediatric Guidelines" also emphasize ICP and CPP control. However, several lines of clinical evidence from studies that use cerebral microdialysis, positron emission tomography, or magnetic resonance imaging show that secondary brain injury is not always associated with perturbations in ICP or CPP and that mechanisms other than simple perfusion-limited anomalies may lead to cellular injury after TBI [5, 13, 20, 21, 23, 37, 40, 48].

It is thought that when recognized early, the correction of secondary insults can help improve patient outcome. Reliable neuromonitoring is necessary to identify secondary cerebral insults. In recent years, direct brain oxygen ($PbtO_2$) monitoring has become feasible. Several observational studies suggest that reduced $PbtO_2$ is associated with poor outcome [13, 22, 39, 43, 46, 47, 51]. Accumulating experimental and clinical evidence also suggest that treatment to increase or fix $PbtO_2$ may improve TBI outcome [14, 22, 26, 35, 39, 42]. Precisely what $PbtO_2$ in humans measures is only now beginning to be elucidated [30]. However, several studies show that $PbtO_2$ is influenced by a wide range of variables including the inspired fraction of oxygen (F_iO_2), arterial partial pressure of oxygen (P_aO_2), mean arterial pressure (MAP), CPP, cerebral blood flow (CBF), and hemoglobin concentration (Hb), to name a few. These studies have, in large part, been performed in adults and less is known about $PbtO_2$ in pediatric TBI. In particular, the relationships between $PbtO_2$ and other markers of secondary brain insults used more commonly in the ICU are not well defined. Therefore, in this study, we examined the relationships between $PbtO_2$ and (1) other physiological markers of potential secondary insults commonly used in pediatric TBI, in particular ICP, CPP and systemic hypoxia, and (2) other clinical factors such as age, Glasgow Coma Score (GCS), and treatment received that may influence $PbtO_2$.

Materials and methods

Ethics approval for the study was obtained from the Institutional Review Boards of the Red Cross Children's Hospital and the University of Cape Town.

Patient selection Data from a consecutive series of pediatric patients who underwent $PbtO_2$ and ICP monitoring for severe TBI at Red Cross Children's Hospital from June 2006 to May 2008 were prospectively collected. Patients included in this study were all less than 15 years old and were considered for intracranial monitoring if their post-resuscitation GCS was ≤8 or deteriorated to this level after admission. Patients did not undergo intracranial monitoring if extubation was planned early for an improving patient or brain death was imminent [GCS 2T/15, fixed and dilated pupils, and 'black brain' on computed tomography (CT) head scan]. Patients were resuscitated, underwent endotracheal intubation, and were mechanically ventilated in the pediatric ICU. Each child was managed according to a local algorithm based on the current recommendations for the management of severe TBI in children [1]. Details of this management are described in Part I.

Admission clinical factors At admission, we recorded the initial MAP, whether there was initial hypoxia [P_aO_2< 60 mmHg (8 kPa)], whether the initial systolic blood pressure was <90 mmHg and if there was polytrauma or an isolated TBI. Other recorded variables included age, gender, postresuscitation GCS, motor component of the GCS, Pediatric Index of Mortality score [36], Pediatric Trauma Score (PTS) [41], and pupillary reactivity.

Intracranial monitors Each patient included in this study received an ICP monitor [Codman ICP Express (Codman, Raynham, MA, USA) or Camino (Integra Neurosciences, Plainsboro, NJ, USA)] and a $PbtO_2$ monitor (Licox®, Integra Neurosciences). The $PbtO_2$ monitors were placed into normal-appearing right frontal white matter based on the admission head CT scan if there were no localized lesions or in the hemisphere with the greater swelling or number of focal lesions.

Physiological variables Intracranial monitoring was started as soon as possible after ICU admission and was continued until ICP and $PbtO_2$ were controlled for >48 h or until the patient died. The first 2 h of data were discarded to allow for probe stabilization. Terminal data (defined as data

recorded after the diagnosis of brain death or when $PbtO_2$= 0 mmHg for >1 h) were not included in the analysis. The duration of monitoring was recorded for each patient. The following physiological data were collected.

$PbtO_2$ The following $PbtO_2$ values were calculated for each patient: lowest $PbtO_2$ recorded during the monitored period ($PbtO_{2_{low}}$), mean $PbtO_2$ during the first 24 h of monitoring ($mPbtO_{2_{24}}$), and the number of episodes of $PbtO_2$< 10 mmHg ($PbtO_{2_{<10}}$) or $PbtO_2$<5 mmHg ($PbtO_{2_{<5}}$) experienced. Because brain injury is associated with the depth and duration of brain hypoxia, we also defined a measure of low $PbtO_2$ to reflect this. Therefore, for each episode that $PbtO_2$ was <10 mmHg ($PbtO_2$=X mmHg) in each patient, we calculated the value $10-X$ mmHg. Because a $PbtO_2 \leq 10$ mmHg is thought to be a critical tissue hypoxia threshold [33, 43], the value $10-X$ was used to represent the depth of hypoxia. Thereafter, we averaged all of these ($10-X$) values from each patient. This average was then multiplied by the number of episodes that $PbtO_2$ was less than 10 mmHg in that patient. This was termed the time–severity product to reflect the overall brain hypoxia burden.

Intracranial pressure The following ICP values were recorded for each patient: mean ICP for the duration of monitoring (mICP), mean ICP for the first 24 h of monitoring ($mICP_{24}$), the number of episodes that ICP was >20 mmHg ($ICP_{>20}$), the mean of all episodes that ICP was >20 ($mICP_{>20}$), and the highest ICP (ICP_{peak}) experienced.

Cerebral perfusion pressure CPP values that were calculated for each patient included the following: initial CPP ($CPP_{initial}$), the lowest CPP experienced (CPP_{low}), and the number of episodes of CPP<40 mmHg ($CPP_{<40}$) and CPP<50 mmHg ($CPP_{<50}$) experienced.

Systemic oxygenation Systemic hypoxia was defined as P_aO_2<8 kPa (60 mmHg) on arterial blood gas (ABG), or arterial saturation of oxygen (S_aO_2) <90% on peripheral oximetry or ABG. The lowest P_aO_2 ($P_aO_{2_{low}}$) observed also was recorded.

Hemoglobin Arterial Hb was recorded as initial Hb ($Hb_{initial}$), lowest Hb (Hb_{low}), and mean Hb for the duration of the ICU stay (mHb).

Treatment factors Treatment factors that were evaluated included red blood cell transfusion, use of hypertonic saline (number of times given), decompressive hemicraniectomy performed, use of thiopentone, and the use of inotropes to elevate BP.

Data collection and statistical analysis Continuously monitored data were recorded as time-linked hourly variables. Secondary cerebral insults were defined as ICP>20 mmHg, CPP<50 mmHg, Hgb<8 g/dl, and P_aO_2<8 kPa. The relationships between $PbtO_2$ and these secondary insults and the physiological variables described above were compared. In general, comparisons were made using categorical variables relating secondary insults to $PbtO_2$ or brain hypoxia ($PbtO_2$<10 or <5 mmHg). In addition, comparisons between raw observations of $PbtO_2$ and other continuous and intermittent monitoring variables were made where possible.

All data were analyzed with *R* statistical computing (http://wwww.r-project.org) and Stata software (version 7.0, College Station, TX, USA). Potential secondary insults of ICP, CPP, systemic hypoxia, and anemia were recorded as numbers of episodes (of abnormal values) or as absolute values and were compared with similarly recorded potential $PbtO_2$ insults. Spearman's correlation coefficients were used to test correlation between $PbtO_2$ and other physiological and clinical factors. Raw observations for $PbtO_2$ were also compared to time-linked corresponding values for ICP, CPP, P_aO_2, S_aO_2, arterial carbon dioxide tension (P_aCO_2), and Hb. Significance was set at p=0.05. Descriptive statistics are reported as mean±SD or median and interquartile range (IQR) depending on distribution characteristics.

Results

Clinical characteristics Fifty-two pediatric patients between 9 months and 14 years of age (mean age, 6.5± 3.4 years) with severe TBI (GCS≤8) received monitoring for ICP, CPP, and $PbtO_2$ between June 2006 and May 2008. The baseline demographic and clinical variables of this patient cohort are described in Part I. The median duration of invasive monitoring was 5 days (IQR, 3–7 days). A total of 5,619 h of $PbtO_2$ monitoring was analyzed, of which 5,510 h had complete time-linked datasets for $PbtO_2$, ICP, and CPP.

Summary of physiological variables Table 1 lists summary values and the frequency of potential secondary insults for the measured physiological factors. Mean $PbtO_2$ was 34± 13 mmHg. Episodes of $PbtO_2$<10 mmHg occurred in 27 patients (52%) and $PbtO_2$<5 mmHg occurred in 12 patients (23%). The medians (IQR) for the lowest $PbtO_2$ and $mPbtO_{2_{24}}$ were 10 mmHg (6–17 mmHg) and 28 mmHg (22–35 mmHg), respectively. Episodes of ICP>20 mmHg occurred in 43 patients (83%) and CPP<50 mmHg in 38 patients (73%). Episodes of P_aO_2<8kPa occurred in 12 patients (23%) and S_aO_2<90% in 18 patients (35%).

Table 1 Summary of physiological variables

Characteristic	Value
$PbtO_2$	
$PbtO_{2_{low}}$	9.7 (6.4–16.8), range 0–28.3
$PbtO_2$<5 (episodes)	0 (0–0), range 0–20
$PbtO_2$<5 (number of patients)	12 (23%)
$PbtO_2$<10 (episodes)	1 (0–2), range 0–22
$PbtO_2$<10 (number of patients)	27 (52%)
$mPbtO_{2_{24}}$ (mmHg)	28.3 (22.3–34.8), range 0.6–53
ICP	
ICP_{peak} (mmHg)	31 (22–44), range 9–76
$mICP_{24}$ (mmHg)	14 (11–18), range 3–60
$mICP_{total}$ (mmHg)	14 (12–16), range 3–60
$ICP_{>20}$ (episodes)	6 (1–25), range 0–128
$ICP_{>20}$ (number of patients)	43 (83%)
$mICP_{>20}$ (mmHg)	24 (22–27), range 0–61
CPP	
CPP_{low} (mmHg)	43 (33–50), range 0–73
CPP<40 (episodes)	0 (0–2), range 0–24
CPP<40 (number of patients)	20 (38%)
CPP<50 (episodes)	3 (0–12), range 0–77
CPP<50 (number of patients)	38 (73%)
P_aO_2	
P_aO_2<8 (episodes)	0 (0–0), range 0–16
PaO2<8 (number of patients)	12 (23%)
$P_aO_{2_{low}}$ (kPa)	10.4 (8.4–13), range 5.5–38.3
S_aO_2	
$S_aO_{2_{<90}}$ (episodes)	0 (0–1), range 0–9
$S_aO_{2_{<90}}$ (number of patients)	18 (35%)
Hb	
Hb_{low} (g/dl)	8.8 (7.9–9.3), range 6–13.6

N=5,619 h examined, terminal data excluded. Values are expressed as median (IQR) and range of the values, number of episodes above or below thresholds for all patients, or as the number of patients (percent) who experienced values above or below the respective thresholds as appropriate. See "Materials and methods" for abbreviations

Relationships between $PbtO_2$ and admission clinical factors The Spearman's correlation coefficients and corresponding *p* values that describe the associations between $PbtO_2$ parameters ($PbtO_{2_{low}}$, $PbtO_2$<5, $PbtO_2$<10, and $mPbtO_{2_{24}}$) and admission clinical factors are shown in Table 2. No variable was significantly associated with all $PbtO_2$ parameters, but individual associations were found with initial GCS ($PbtO_2$<5, p=0.0113) and PTS ($PbtO_2$<10, p=0.0175).

Relationships between $PbtO_2$ and physiological variables The Spearman's correlation coefficients and corresponding *p* values that describe the associations between $PbtO_2$ parameters and physiological monitored variables are reported in Table 3. No variable was significantly associated with all $PbtO_2$ parameters, but individual associations were found with initial $mICP_{>20}$ ($mPbtO_{2_{24}}$, p=0.04), CPP_{low} ($PbtO_{2_{low}}$, p=0.007), CPP<40 ($PbtO_{2_{low}}$, p=0.03; $PbtO_2$<5, p=0.02), P_aO_2<60 ($mPbtO_{2_{24}}$, p=0.004), and S_aO_2<90 ($PbtO_{2_{low}}$, p=0.04).

Relationships between $PbtO_2$ and treatment variables The use of inotropes was associated with $PbtO_{2_{low}}$, (p=0.03), $PbtO_{2_{<10}}$ (p=0.03), and $mPbtO_{2_{24}}$ (p=0.03). No other treatment variable demonstrated any relationship with $PbtO_2$ measures (Table 4).

Relationships between raw observations of $PbtO_2$ and physiological variables $PbtO_2$ had significant relationships with ICP, CPP, P_aO_2, S_aO_2, and Hb, but the corresponding correlation coefficient for each of these was weak (Table 5). $PbtO_2$ had no relationship with P_aCO_2. Of note, although the correlation coefficient was small, the regression line for the relationship between $PbtO_2$ and ICP was positive, not negative (Fig. 1); only the nonparametric line tended toward decreased values of $PbtO_2$ with values of ICP> 40 mmHg.

Discussion

In this study that included 52 children (<15 years old) with severe TBI, we examined the relationships between $PbtO_2$ and other physiological, clinical, and treatment factors that are used to guide therapy and predict outcome. These relationships were examined using time-linked raw observations and by categorizing the data into secondary cerebral insults. The main findings were the following: (1) reduced brain oxygen is poorly predicted by clinical and physiological factors commonly measured in pediatric ICU care, and (2) there is a weak relationship between raw observations of $PbtO_2$ and time-linked ICP, CPP, S_aO_2, P_aO_2, and Hb. These findings are important and consistent with observations in adults [15, 23, 40, 47] and suggest that brain hypoxia may still occur despite apparently "adequate" resuscitation and therapy of pediatric TBI based on current guidelines, implying that therapy directed solely by ICP and CPP management may not be optimal for avoiding brain hypoxia. These data imply that multi-modality monitoring may need to be considered in children with severe TBI. However, whether this makes a difference to outcome will require additional study.

Methodological limitations There are several potential limitations to this study. First, the sample size (n=52) is relatively small, and so our results should be regarded as

Table 2 The Spearman's correlation coefficients (p value) for admission clinical factors and $PbtO_2$ parameters

	$PbtO_{2_{low}}$	$PbtO_2<5$	$PbtO_2<10$	$mPbtO_{2_{24}}$
Initial GCS	0.21 (0.1404)	−0.35 (0.0113)[a]	−0.26 (0.0625)	0.03 (0.8545)
Motor GCS	0.17 (0.2307)	−0.11 (0.4576)	−0.21 (0.1378)	0.14 (0.3279)
Gender	−0.15 (0.2903)	0.002 (0.9887)	0.15 (0.2829)	−0.20 (0.1495)
Age	0.21 (0.1429)	−0.01 (0.9327)	−0.01 (0.9276)	0.041 (0.7748)
PTS	−0.15 (0.2817)	0.10 (0.4709)	0.33 (0.0175)[a]	−0.08 (0.566)
PIM 2	−0.07 (0.6208)	0.11 (0.4568)	0.07 (0.6012)	−0.09 (0.5321)
CT class	−0.07 (0.6286)	0.09 (0.5474)	−0.02 (0.8974)	0.04 (0.7652)
Pupils	−0.24 (0.0833)	0.23 (0.108)	0.22 (0.1236)	0.017 (0.9074)
Initial hypoxia	0.03 (0.8548)	0.07 (0.6193)	0.01 (0.9481)	0.08 (0.5686)
Initial MAP	−0.01 (0.948)	−0.07 (0.6087)	0.08 (0.5577)	−0.07 (0.6011)
Initial SBP<90	−0.01 (0.9171)	0.02 (0.9101)	−0.04 (0.7724)	−0.02 (0.8923)
Initial Hb	0.04 (0.8021)	−0.04 (0.77)	0.05 (0.6994)	−0.06 (0.6498)
Polytrauma	0.05 (0.7315)	0.05 (0.7342)	−0.02 (0.882)	−0.11 (0.4349)

CT class CT classification, *SBP* systolic blood pressure

[a] Significant results

preliminary. However, more than 5,000 time-linked data points were examined, suggesting that the findings are robust. Second, while the patients represent a relatively homogeneous cohort of children less than 15 years old, the age range covers significant differences in physiological profiles (9 months to 14 years old). It is conceivable that this may bias our results, since there may be age-related differences in the relationships between $PbtO_2$ and other physiological factors. In addition, we cannot define physiological thresholds according to specific ages. Third, this was not a pure observational study in that low $PbtO_2$, high ICP, and low CPP were treated. This may bias our results because untreated secondary insults may have different associations with physiological factors than treated secondary insults. Fourth, $PbtO_2$ is a focal measure of brain oxygenation. However, when $PbtO_2$ is measured in normal-appearing white matter, the value appears to reflect global brain oxygenation [18, 19, 31, 33, 45]. Fifth, $PbtO_2$ is determined in part by CBF [17, 30, 44]; CBF and $PbtO_2$ may vary over time after severe TBI. While this may influence our results, we think it unlikely because of the various methods we used to examine the relationship between $PbtO_2$ and the multiple clinical and physiological variables. Despite these limitations, we believe that our results indicate that even when physiological and clinical characteristics commonly used in pediatric TBI are "normal," brain hypoxia, i.e., a secondary cerebral insult, may still occur. In particular, the relationships between both secondary insults and raw observations of $PbtO_2$ and other clinical and physiological factors were weak; therefore, assumptions about brain oxygen cannot be reliably made based on other physiological or clinical variables. These data imply that multimodality monitoring may be needed to complement therapy of pediatric TBI.

Table 3 The Spearman's correlation coefficients (p value) for physiological factors/ secondary insults and $PbtO_2$ parameters

	$PbtO_{2_{low}}$	$PbtO_2<5$	$PbtO_2<10$	$mPbtO_{2_{24}}$
$ICP_{>20}$	−0.09 (0.5105)	0.02 (0.8658)	0.06 (0.6641)	0.05 (0.7091)
$mICP_{>20}$	0.03 (0.8592)	0.07 (0.604)	−0.04 (0.7821)	0.29 (0.0377)[a]
ICP_{peak}	−0.09 (0.4897)	0.11 (0.4421)	0.09 (0.5087)	0.15 (0.296)
$mICP_{24}$	−0.18 (0.1989)	0.21 (0.1258)	0.14 (0.3294)	0.16 (0.2518)
mICP	−0.18 (0.2121)	0.19 (0.1876)	0.12 (0.396)	0.15 (0.2801)
CPP_{low}	0.38 (0.0065)[a]	−0.26 (0.0641)	−0.27 (0.054)	0.06 (0.6512)
$CPP_{<40}$	−0.31 (0.0269)[a]	0.32 (0.0212)[a]	0.19 (0.1702)	−0.09 (0.5394)
$CPP_{<50}$	−0.23 (0.1093)	0.10 (0.4683)	0.1 (0.3227)	−0.07 (0.6211)
$P_aO_{2_{<60}}$	−0.22 (0.1193)	0.25 (0.0789)	0.20 (0.1463)	−0.40 (0.0037)[a]
$P_aO_{2_{low}}$	0.06 (0.6541)	0.01 (0.9495)	−0.04 (0.7602)	0.26 (0.0618)
$mPaO_2$	−0.24 (0.0841)	0.26 (0.0584)	0.14 (0.318)	−0.01 (0.9559)
$S_aO_{2_{<90}}$	−0.28 (0.0438)[a]	0.27 (0.0544)	0.27 (0.0569)	−0.20 (0.1616)
Hb_{low}	0.09 (0.5409)	−0.18 (0.1943)	−0.03 (0.8292)	0.09 (0.5238)
mHb	−0.16 (0.268)	0.01 (0.9209)	0.07 (0.629)	−0.13 (0.3641)

[a] Significant results

Table 4 The Spearman's correlation coefficients (p value) for treatment factors and $PbtO_2$ parameters

	$PbtO_2$	PbtO2<5	$PbtO_2$<10	$mPbtO_{2_{24}}$
Duration	−0.04 (0.8249)	−0.05 (0.7139)	0.041 (0.7753)	−0.15 (0.2728)
RBCT	−0.08 (0.5951)	0.12 (0.3733)	−0.02 (0.9113)	−0.18 (0.2038)
HTS	−0.16 (0.2537)	0.041 (0.7758)	0.11 (0.426)	−0.14 (0.3254)
DC	−0.05 (0.7076)	−0.10 (0.465)	0.13 (0.3411)	0.07 (0.6168)
Thiopentone	0.07 (0.6387)	−0.16 (0.2477)	0 (1)	−0.13 (0.3581)
Inotropes	−0.31 (0.0276)[a]	0.10 (0.461)	0.31 (0.0277)[a]	−0.31 (0.0276)[a]

Duration length of invasive monitoring, *RBCT* red blood cell transfusion, *HTS* hypertonic saline (number of times used), *Thiopentone* use of thiopentone for ICP control, *DC* decompressive craniectomy used, *Inotropes* use of inotropes to increase blood pressure

[a] Significant results

What is associated with $PbtO_2$ after pediatric TBI? $PbtO_2$ is influenced by a wide range of variables such as F_iO_2, P_aO_2, MAP, CPP, CBF, and Hb. Recent studies in adult TBI [30] suggest that $PbtO_2$ reflects the product of CBF and the arteriovenous difference in oxygen tension. We did not measure CBF and so do not know whether this relationship also is true in pediatric TBI. Nevertheless, our results do show interesting and important relationships. For example, we observed an association between episodes of low $PbtO_2$ and the lowest CPP, episodes of CPP<40 mmHg, episodes of P_aO_2<60 mmHg, and episodes of S_aO_2<90%.

The association between $PbtO_2$ and measures of arterial oxygenation is not surprising because systemic hypoxia is a known secondary insult that may aggravate TBI outcome [8, 27]. Furthermore, $PbtO_2$ is a measure of oxygen tension; therefore, it can be influenced by arterial oxygen pressure [24, 30]. However, in children with severe TBI, normal lung function and normal systemic oxygenation do not mean that $PbtO_2$ is normal. Instead, when these parameters are abnormal and $PbtO_2$ is reduced, then therapy may be better targeted to the cause.

Reduced $PbtO_2$ also was associated with CPP< 40 mmHg, but not with a CPP<50 mmHg. On the other hand, episodes of low $PbtO_2$ occurred despite CPP> 50 mmHg. These are important observations because the optimal CPP for pediatric patients with head injury is poorly defined. The current guidelines for the management of severe pediatric TBI recommend that CPP be maintained greater than above 50 mmHg. However, this recommendation is considered an option, rather than a "guideline". Furthermore, age-appropriate CPP may represent a continuum [3]. Whether the additional information provided by a $PbtO_2$ monitor will help determine age appropriate CPP will need further study. It is our opinion however that a $PbtO_2$ monitor can help select the appropriate CPP for an individual patient. This is important because CPP-based therapy may have a deleterious effect on the lungs [9, 29] and so aggravate outcome.

The association between $PbtO_2$ and the use of inotropes most likely reflects attempts by the treating clinician to increase BP in response to low $PbtO_2$ as a therapeutic maneuver.

Intracranial pressure and brain oxygen An ICP monitor is considered the "gold standard" monitor in TBI care in the

Table 5 Spearman's correlation between raw observations of $PbtO_2$ and other factors

Characteristic	Coefficient	p value	Number of observations
ICP	0.0804	<0.0001	5,510
CPP	0.0655	<0.0001	5,510
P_aO_2	0.0830	0.0201	785
P_aCO_2	−0.0311	0.3915	760
Hb	0.1337	0.0275	272
S_aO_2	0.0727	<0.0001	5,354

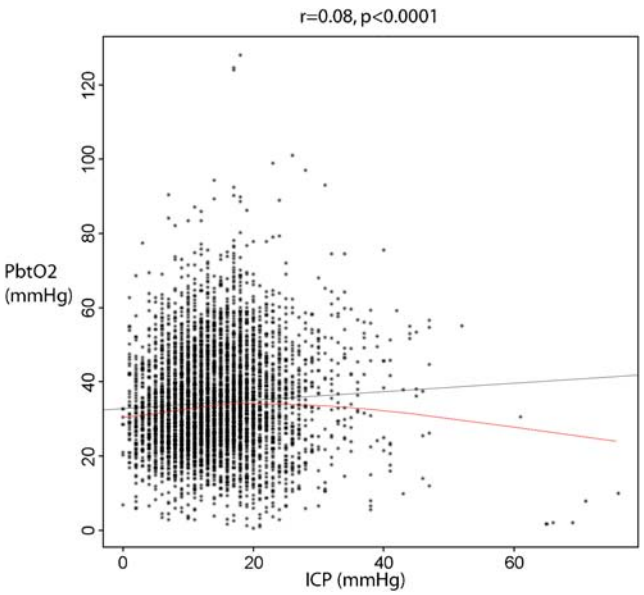

Fig. 1 Scatterplot matrix for $PbtO_2$ and ICP showing the regression line for the relationship between ICP and $PbtO_2$ (*black line*) and the nonparametric line (*pink line*). ICP and $PbtO_2$ in mmHg

ICU. Recent studies suggest that ICP is more than a number, and useful information about brain compliance and autoregulation can be obtained from derived indices of cerebrovascular reactivity and cerebrospinal compensatory reserve [38]. By contrast, some authors suggest that there may be little benefit to TBI therapy based on ICP monitoring [4, 10, 11, 34]. Our study shows a weak relationship between ICP and $PbtO_2$. Among the various ICP parameters that we examined, only mean ICP greater than 20 mmHg had a relationship with mean $PbtO_2$. This relationship was evident in the first 24 h after injury. Although the correlation coefficient between ICP and $PbtO_2$ in our study was weak, the slope of the regression line between ICP and $PbtO_2$ was positive, which is unexpected. This may reflect the association of both measures with hyperemia. The expected decline of $PbtO_2$ was observed only when ICP was severely elevated (>40–50 mmHg) but not with moderately elevated ICP, and episodes of low $PbtO_2$ occurred despite normal ICP. This is consistent with previous findings that maintaining the thresholds for ICP and CPP described in the adult and pediatric "Guidelines" do not necessarily avoid brain hypoxia in all patients [13, 40]. These data do not imply that an ICP monitor should not be used. Instead, they suggest that the threshold at which ICP should be treated and the methods best suited to do so may require interpretation based on complementary modalities of monitoring such as $PbtO_2$ [16, 32] to best target therapy for the individual patient and his or her specific pathophysiology. This is important because every treatment for ICP also has potential deleterious side effects.

Conclusion In summary, conventional physiological variables (e.g., ICP and CPP) and clinical factors have weak relationships with $PbtO_2$ after pediatric TBI. This limited relationship is true whether raw time-linked variables or categorical variables that describe secondary cerebral insults are examined. The data emphasize the complex and heterogeneous nature of brain pathophysiology after TBI. In addition, these results have important implications in the care of severe TBI, since there is a significant independent association between reduced $PbtO_2$ and poor outcome. Our data suggest that the relationships between $PbtO_2$ and ICP, CPP, and systemic oxygenation, among others are complex and require further investigation. However, we believe that the data also suggest that multimodality monitoring should be considered to best understand individual patient pathophysiology after severe pediatric TBI.

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