Original Paper

Pediatric Neurosurgery

Pediatr Neurosurg 1997;26:200–207

Received: February 14, 1997
Accepted after revision: August 11, 1997

P. David Adelson
Brent Clyde
Patrick M. Kochanek
Stephen R. Wisniewski
Donald W. Marion
Howard Yonas

Departments of Pediatric Neurosurgery, Anesthesiology and Critical Care Medicine, Children's Hospital of Pittsburgh, Safar Center for Resuscitation Research, and Department of Public Health and Biostatistics, University of Pittsburgh, Pa., USA

Cerebrovascular Response in Infants and Young Children following Severe Traumatic Brain Injury: A Preliminary Report

Abstract

To further describe the pathophysiologic processes that occur in infants and young children after severe traumatic brain injury (TBI), we retrospectively reviewed the cerebral blood flow (CBF) values and 6-month Glasgow Outcome Scores (GOS) in 30 children ≤8 years old (25 were ≤4 years old) with a Glasgow Coma Score (GCS) on admission of ≤8. Twelve females and 18 males (mean age 2.1 years, range 1 month to 8 years) underwent 61 CBF studies using stable xenon computed tomography at variable times from admission to 9 days after TBI. In 12 patients, $PaCO_2$ was manipulated an average of 8.4 torr (range 5–11 torr) and a second CBF study performed to determine CO_2 vasoreactivity (CO_2VR), defined as the percent change in CBF per torr change in $PaCO_2$. CBF on admission (n = 13) was 25.1 ± 7.7 ml/100 g/min (mean ± SEM) and was ≤20 ml/100 g/min in 10 of 13 patients (77%). By 24 h and for up to 6 days after TBI, the mean CBF increased to 55.3 ± 3.4 ml/100 g/min (range 2–95) which differed significantly from the admission CBF value ($p < 0.05$); a CBF of >70 ml/100 g/min tended to be associated with a good outcome. Poor outcome (GOS ≤3) was seen uniformly in children under the age of 1 year and in patients with a CBF of ≤20 ml/100 g/min any time after TBI. Poor outcome was seen in 85% of children under the age of 24 months, but in only 41% of children ≥24 months old. Mean CO_2VR was 2.1 ± 0.6%/torr $PaCO_2$ and ranged from 0.02 to 5.98%. Mean CO_2VR tended to differ between good and poor outcome children (3.2 ± 0.9 and 1.17 ± 0.2%, respectively) and a CO_2VR of ≤2% was significantly associated with a poor outcome. Younger age, low CBF in the early period after TBI, and a CO_2VR of <2% was associated with a poor outcome in this subgroup of children. Young children (<24 months) may represent a particular high-risk group with early hypoperfusion after severe TBI. This finding may be a key factor in the pathophysiology and outcome in this age group, and may need to be addressed in our future therapeutic protocols.

Key Words
Head injury
Cerebral blood flow
Xenon computed tomography

Introduction

Trauma, and in particular, traumatic brain injury (TBI) are major causes of death and disability in children. Since the primary neural injury is not amenable to treatment except through preventative measures, the goals of future intervention depend on increasing our understanding of the pathophysiologic response to the injury. In this way, therapeutic modalities may be developed in an attempt to interrupt the secondary injury phase and improve outcome. Though children overall have better outcomes than adults following injury, mortality is particularly high in the subgroup of children less than 4 years of age [1]. As well, several important studies have shown that the young survivors of severe TBI, suffer worse functional outcomes in the areas of intellectual (cognition and memory) and motor functions compared to older children [2, 3]. Levin et al. [3] commented that this subgroup of patients may be particularly important since they seem to be more susceptible to long-term functional deficits. Whether this is due to differences in the mechanism of injury or inherent age-related physiologic differences remains unclear.

Though there are a few important studies that have reported on the changes in cerebral blood flow (CBF) in children following TBI [4–6], none of the studies specifically addressed the cerebrovascular response in infants

KARGER

E-Mail karger@karger.ch
Fax + 41 61 306 12 34
http://www.karger.ch

This article is also accessible online at:
http://BioMedNet.com/karger

P. David Adelson, MD
Department of Pediatric Neurosurgery
Children's Hospital of Pittsburgh, 3705 Fifth Avenue
Pittsburgh, PA 15213-2583 (USA)
Tel. +1 412 692 6347, Fax +1 412 692 5921, E-Mail david-adelson@POPLAR.chp.edu

and young children since very few patients in this subgroup were studied. In this preliminary report, we present the results of a serial study of global and regional CBF and cerebrovascular reactivity to changes in $PaCO_2$, using the xenon computed tomography (XeCT) method in infants and young children who suffered a severe TBI. Twenty-five children were <4 years, which represents the younger subset of patients of an ongoing study of CBF in children in our center. For this report, we focused on two goals: (1) to define the changes in CBF and CO_2 vasoreactivity (CO_2VR) in this pediatric age subgroup, and (2) to understand the relationship between these variables and outcome.

Clinical Materials and Methods

Study Population

We retrospectively analyzed data from the charts of all of the children referred and admitted to the Children's Hospital of Pittsburgh from January 1989 until July 1996 with the diagnosis of severe TBI (Glasgow Coma Score, GCS, ≤8 at time of admission) who underwent a CBF study using the XeCT method. Since we were specifically interested in young children, only the 30 children (of our larger database of children with TBI) that were ≤8 years old at the time of injury were included for analysis. The children were further stratified by age: group I, <12 months (n = 8); group II, 12–23 months (n = 5); group III, 24–47 months (n = 12), and group IV, 48–96 months (n = 5). The clinical record, including the emergency room, intensive care unit, acute care facility and outpatient records, were reviewed for the history, hospital course, physiological variables at the time of the CBF study, and outcome. Following admission to the emergency department, the severity of the injury was scored for all of the children using the GCS (modified to the children's GCS) and a CT scan of the head was obtained to determine the radiologic diagnosis of the injury. We defined the predominant injury as either a 'focal' injury (a focal lesion of >5 mm in diameter including subdural or epidural hematomas, contusion, or unilateral hemispheric injury with mass effect or shift) or a 'diffuse' injury if there was no focal lesion of >5 mm or bilateral swelling or injury noted radiologically on CT [7]. The incidence of intracranial hypertension (intracranial pressure, ICP, of >20 mm Hg for >5 min) was also noted. Each of the patients was managed using our standard head injury protocol [8] which includes placement of an ICP monitor (most often a ventriculostomy) and progressive treatment of intracranial hypertension with sedation, paralysis, cerebrospinal fluid drainage, mild hyperventilation ($PaCO_2$ 32–35 torr), osmotic diuresis, and barbiturates. There were no age-dependent differences in treatment.

Stable XeCT Methodology

CBF studies were obtained at the time of admission with the initial head CT up to 9 days after TBI. The XeCT method was developed, in large part, at the University of Pittsburgh and rapidly became standard in the management of all adults and children after severe TBI requiring neurointensive care. These data were thus readily available for the analysis. We have previously described the XeCT methodology in detail [9]. Briefly, the initial head CT scan was obtained using a GE 9800 CT scanner for anatomic diagnosis and localization. Following inhalation of stable Xe gas (33%) and oxygen (67%) for 4.5 min, four CT scans were performed at each of the three standard scanning levels: the first scan localized to pass through the basal ganglia and the midportion of the third ventricle; the other two levels were obtained 2 cm above and below, respectively.

Table 1. Modified Glasgow Outcome Score (GOS) for children

GOS		Description
5	Good outcome	Good outcome with minimal to no dysfunction, return to school, independent age-appropriate activities, or continuing to achieve age-appropriate milestones
4	Moderately disabled	Notable motor or cognitive dysfunction requiring ongoing therapy, special education, or early intervention; occasionally able to independently perform age-appropriate activities; gaining milestones though delayed
3	Severely disabled	Significant and gross motor or cognitive dysfunction requiring ongoing therapy, special schooling, or early intervention; minimal gaining of age-appropriate milestones
2	Vegetative	No interaction or cognition of outside stimuli
1	Dead	Dead

For each scanning level, a CBF map was then generated with up to 20 contiguous multiple regions of interest (ROIs; 2 cm in diameter) around the cortical mantle, the basal ganglia and the thalamus bilaterally. CBF was calculated simultaneously using commercially available XeCT CBF software (Diversified Diagnostics Products, Houston, Tex.) [10, 11]. Regional and hemispheric CBFs were then calculated from the average of all the ROIs within a specific vascular territory or hemisphere and global CBF was defined as the average of all the ROIs. Arterial samples obtained prior to each CBF study were analyzed for pH, PaO_2, and $PaCO_2$. After obtaining the baseline $PaCO_2$, the end-tidal CO_2 was monitored constantly using a capnograph to ensure stability of the $PaCO_2$ throughout the study. No correction of CBF for $PaCO_2$ was performed. Other physiologic parameters including mean arterial pressure and ICP were also recorded.

CO_2 Vasoreactivity

To determine the responsiveness of CBF to alterations in $PaCO_2$ following TBI, a repeat XeCT study was obtained after altering the tidal volume and/or respiratory rate on the ventilator to change $PaCO_2$ relative to the initial arterial blood gas. A second CBF study was performed at least 15 min after the first and after confirmation of the change in $PaCO_2$ by arterial blood gas measurement. These two-stage studies were used to determine the CO_2VR and were obtained in the first 48 h. CO_2VR was calculated using the previously defined equation by Obrist et al. [12] which determines the percent change in CBF for each torr change in $PaCO_2$:

$$CO_2VR = \frac{(CBF_1 - CBF_2)}{CBF_1} \times 100/PaCO_{2(1)} - PaCO_{2(2)},$$

CO_2VR = (% change in CBF/torr change in $PaCO_2$).

Table 2. Patient demographic and clinical data

Patient No.	Age, years	Sex	Mechanism	GCS	Initial CT	ICH	Barb	GOS
Group I								
1	0.08	f	MVA	7	diffuse	yes	yes	3
2	0.08	m	abuse	6	diffuse	yes	no	3
3	0.1	f	abuse	3	diffuse	yes	yes	3
4	0.1	f	MVA	4	diffuse	yes	yes	3
5	0.16	m	abuse	3	diffuse	yes	yes	1
6	0.22	m	MVA	3	diffuse	yes	yes	3
7	0.25	f	abuse	3	diffuse	yes	no	1
8	0.42	f	abuse	3	diffuse	yes	no	1
Group II								
9	1	m	MVA	3	diffuse	yes	no	1
10	1.04	m	abuse	6	focal	yes	yes	3
11	1.1	m	abuse	7	focal	no	no	4
12	1.3	m	abuse	3	diffuse	yes	no	5
13	1.9	m	MVA ped	8	focal	yes	yes	3
Group III								
14	2.08	f	abuse	4	focal	yes	yes	3
15	2.14	f	abuse	4	diffuse	yes	yes	4
16	2.18	m	MVA ped	7	diffuse	yes	yes	4
17	2.2	m	fall	6	focal	yes	no	5
18	2.23	f	MVA	3	diffuse	yes	no	1
19	2.3	m	abuse	3	focal	yes	yes	3
20	2.5	m	abuse	4	focal	yes	yes	3
21	2.66	f	abuse	4	focal	yes	yes	4
22	2.83	m	MVA	6	diffuse	yes	yes	1
23	3.16	f	MVA	6	diffuse	no	no	5
24	3.67	m	projectile	8	focal	yes	no	5
25	3.7	m	fall	5	focal	yes	yes	4
Group IV								
26	4.36	m	MVA ped	8	diffuse	yes	yes	5
27	4.75	m	MVA ped	4	diffuse	no	no	4
28	5.15	f	MVA	5	diffuse	yes	yes	1
29	5.98	f	MVA ped	8	diffuse	no	no	5
30	8	m	MVA	5	diffuse	yes	yes	1

m = Male; f = female; MVA = motor vehicle accident; MVA ped = auto vs. pedestrian; GCS = Glasgow Coma Score; ICH = intracranial hypertension (intracranial pressure ≥ 20 mm Hg); Barb = barbiturates used; GOS = Glasgow Outcome Score.

Outcome Assessment

Neurologic assessment of outcome was determined using the Glasgow Outcome Score (GOS) [13] which we modified for the pediatric age group (table 1) and was obtained a minimum of 6 months after injury. Those patients with good function or only moderately disabled (GOS ≥ 4) were combined into the 'good' outcome category. The 'poor' outcome group included those patients who were either severely disabled, vegetative, or who died (GOS ≤ 3) before their 6-month evaluation.

Statistical Analysis

The means and standard error (SEM) of age, CBF, and CO_2VR were calculated. Data were compared between 'good' and 'poor' outcome using a Fisher's exact test. A t test was used to test the equality of means. Stepwise logistic regression methods were used to identify factors, i.e., age, mechanism of injury, or sex, that may have been independently associated with a good outcome. A probability value of less than 5% ($p < 0.05$) was considered significant.

Results

Thirty children underwent 61 XeCT CBF studies. There were 18 males and 12 females with a median age of 2.08 years (mean age 2.2 ± 0.36 years, range 0.10–8.0 years). The majority of studies (40) were obtained within the first 48 h after admission and two thirds of the studies

Table 3. CBF and outcome (mean ± SEM)

Age group	Average CBF	Average GOS
Group I (n = 8)[1]	34.7 ± 6.4	2.3 ± 0.4
Group II (n = 5)	48.0 ± 11	3.2 ± 0.7
Group III (n = 12)	51.9 ± 5.2	3.5 ± 0.4
Group IV (n = 5)	54.5 ± 4.1	3.2 ± 0.9
Group I + II (n = 13)	38.5 ± 6.0	2.6 ± 0.4
Group III + IV (n = 17)	55.6 ± 4.4	3.4 ± 0.3

CBF = Cerebral blood flow (ml/100g/min); GOS = Glasgow Outcome Score.

[1] See text for group designations.

Table 4. Physiologic parameters for patients at time of the XeCT scan (mean ± SEM)

Outcome	Hematocrit	Mean arterial pressure, mm Hg	$PaCO_2$
Good	31.0 ± 4.3	79.7 ± 7.8	33.5 ± 6.5
Poor	30.1 ± 4.5	76.2 ± 10.5	32.0 ± 4.9

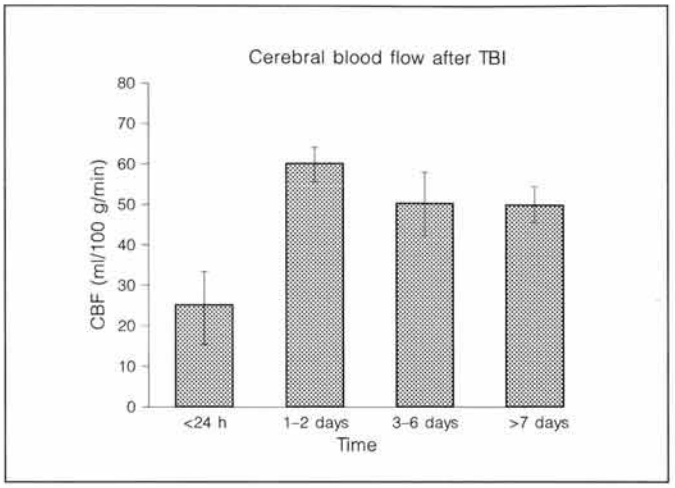

Fig. 1. Cerebral blood flow (CBF) measured by the xenon computed tomographic method in infants and young children versus time after severe traumatic brain injury: <24 h (n = 13); between 1 and 2 days (n = 27); between 3 and 6 days (n = 14), and >7 days (n = 7). CBF was initially low in children assessed <24 h after TBI. Most of the <24 hour studies were performed on admission, during acquisition of the initial CT scan. CBF subsequently increased, peaking at between 1 and 2 days.

were obtained in the first 72 h. The mechanisms of injury included: motor vehicle-related (passenger, vs. bicycle, and vs. pedestrian), falls, penetrating injuries, and abuse/assault. The average GCS on admission was 5.0 (range 3–8), and the admission CT scan revealed a predominance of diffuse injury (67%) compared to focal injury. Intracranial hypertension developed in 26 children (87%). Eighteen children (60%) were aggressively treated using barbiturate infusions, when refractory intracranial hypertension developed.

Twelve children had a 'good' outcome while 18 children had a 'poor' outcome. Poor outcome was seen in all the group-I children and in 85% of those children in groups I and II. A better outcome was observed and was similar in groups III and IV where only 42 and 40% had a poor outcome, respectively (table 2). The proportion of patients with a good outcome increased with age and differed significantly across the 4 age groups (p = 0.032).

CBF Changes following Severe TBI in Infants and Young Children

The admission CBF (n = 13) was 25.1 ± 7.7 ml/100 g/min (range 0–79) and was ≤20 ml/100 g/min in 77% of the patients. By 24 h and up to 6 days after injury, CBF increased to an average of 55.3 ± 3.4 ml/100 g/min (range 2–95), and was highest at 24–48 h (59.6 ± 4.5 ml/100 g/min) before decreasing to <50 ml/100 g/min 3 days after TBI (fig. 1). The children with a good outcome had an early CBF of 43.9 ± 11.0 ml/100 g/min compared to those with a poor outcome (9.9 ± 5.9 ml/100 g/min; $p < 0.05$). The mean CBF for groups I and II and groups III and IV were 38.5 ± 6.0 and 55.6 ± 4.4 ml/100 g/min, respectively (table 3). Considering all studies at all times, CBF was ≤20 ml/100 g/min in 12 patients; all of whom had a poor outcome (fig. 2), and all were <48 months of age (groups I–III). A global CBF of ≤20 ml/100 g/min, anytime in the postinjury phase, was therefore significantly associated with a poor outcome (p = 0.0006) with a sensitivity of 63%, a specificity of 100%, and a positive predictive value of 100%.

A good outcome occurred in a significantly greater proportion of patients with CBF of >55 ml/100 g/min (53%) than those with CBF of ≤55 ml/100 g/min (15%; p = 0.0396), and also tended to occur more frequently in those patients with a CBF of >70 ml/100 g/min (50%) than those with a CBF of ≤70 ml/100 g/min (32%) (p = 0.31; fig. 2). There was no difference in the average $PaCO_2$ between good and poor outcome groups (33.5 ± 6.5 and 32.0 ± 4.9 torr, respectively) or in other physiologic parameters that may have affected CBF values (table 4). Using a multiple logistic regression model, we attempted to identify variables independently associated with a poor

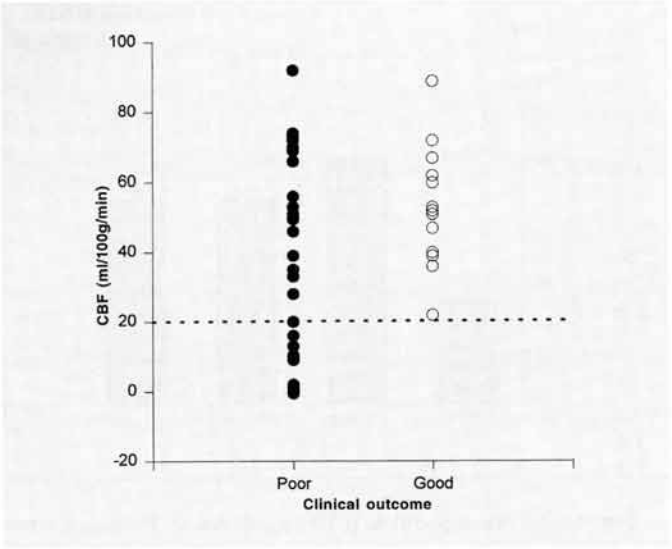

Fig. 2. Cerebral blood flow (CBF) stratified by outcome (good vs. poor) after TBI. Poor outcome was defined as Glasgow Outcome Scale of ≤3. A threshold value of <20 ml/100 g/min was associated with poor outcome ($p < 0.05$). High CBF was seen in patients from both good and poor outcome groups (see text for discussion).

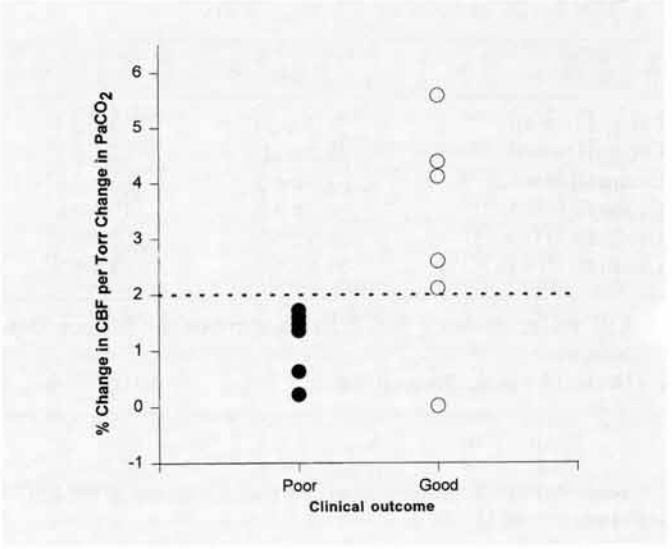

Fig. 3. Global CO_2 vasoreactivity (CO_2VR) stratified by outcome (good vs. poor) in 12 children studied after severe TBI. A global CO_2VR of ≤2% was significant as a threshold for poor outcome ($p = 0.0076$).

outcome. Due to the small sample size and large amounts of variability, a model could not be adequately estimated. A CBF of <20 ml/100 g/min was not significantly different in males vs. females (50 vs. 67%, respectively) or in abuse as a mechanism of injury vs. non-abuse cases (36 vs. 35%, respectively). A CBF of <20 ml/100 g/min did differ ($p < 0.001$) in the percentage of patients ≤2 vs. those >2 years old (82 vs. 31%, respectively).

CO_2VR

Twelve children underwent a two-stage study of CO_2VR of cerebral circulation. Of the children who were studied, there was an even distribution between outcome groups (6/group). The average change in $PaCO_2$ was 8.4 torr (range 5–11 torr) and the mean global CO_2VR was 2.1 ± 0.6% (range 0.02–5.59%). The mean global CO_2VR in the good outcome group was 3.2 ± 0.82% (range 0.02–5.59%) and 1.2 ± 0.24% (range 0.22–1.62%) in the poor outcome group. Though the global CO_2VR in the good outcome group tended to be higher, it did not significantly differ from the poor outcome group ($p = 0.06$). However, a CO_2VR of ≤2% had a sensitivity of 83%, a specificity of 100%, and a positive predictive value of 100% for poor outcome (fig. 3). Global CO_2 nonreactivity (≤2%) was associated with a higher percentage of poor outcomes (100 vs. 15% in patients with a global CO_2VR of >2%; $p = 0.0076$).

Discussion

Although children, in general, have a better outcome compared to adults both in mortality and morbidity, infants and young children (<4 years of age) have particularly poor outcomes after TBI [1]. Because of the lack of studies in this subgroup of children, it is unclear whether this increased susceptibility to poor outcome is due to the mechanism of injury or a unique anatomic and/or physiologic response. Recent studies of CBF in adults [10,12, 14–17] and in older children [5, 6] after TBI suggest that early (<24 h after TBI) low CBF may be associated with poor outcome and 'high' CBF was not associated with outcome. Though these studies were important in the understanding of the response of CBF in children after TBI, very few infants and young children were included, leaving in question the cerebrovascular response of this age group. In the present study, we utilized XeCT to assess the acute changes in CBF and CO_2VR in young children after TBI and found that: (1) CBF was low early after TBI (<24 h) in the poor outcome group; (2) global CBF (≤20 ml/100 g/min) and young age (<2 years) were significantly associated with a poor outcome; (3) higher CBF tended to occur in the good outcome group; (4) CO_2VR tended to be lower in patients with a poor outcome, and (5) CO_2VR ≤2%/torr change $PaCO_2$ was associated with a poor outcome.

Table 5. Previous studies on CBF in children

References	Method	Patients			Findings
		n	age ranges	mean age/years	
Kassoff et al. [11]	^{133}Xe	10	9 months to 12 years	7	6 children had regional increases in CBF
Bruce et al. [4]	^{133}Xe	6	16–21 years		Elevated CBF related to hyperemia and diffuse swelling
Muizelaar et al. [5]	^{133}Xe	32	3–18 years	14	Early low CBF with later relative hyperemia, no correlation to outcome
Sharples et al. [6]	N_2O	21	2–16 years	8	Hyperemia rare, ICP elevations related to low CBF, autoregulation intact
Present report 1997	XeCT	30	0–8 years	2.2	Early low CBF, age and low CO_2VR related to outcome

Infants and Young Children and TBI

Careful review of the classic literature of CBF in pediatric TBI revealed the surprising finding that few of the children in whom CBF was evaluated were <4 years of age (the group with the poorest outcome and the most unique mechanism of injury [child abuse]; (table 5). In the classic study by Bruce et al. [4], using the ^{133}Xe method, the ages of the patients were 16–21 years at the time of injury and no young children were evaluated. Kasoff et al. [11] studied 6 young children (ages 9 months to 12 years) using the ^{133}Xe method in the acute period after injury at variable times after TBI. Their average age was 7 years but the studies were very limited in scope. Sharples et al. [6] reported on 21 children (ages 2–16 years) with a mean age of 8 years, but only 5 children were <4 years old. In the most comprehensive study to date, Muizelaar et al. [5] reported on 32 children following TBI with a mean age of 14 years; however, only 4 of these children were <8 years. Our report thus represents the largest series of CBF data in young children after TBI since the 30 children in this study were all ≤8 years old with a mean age of approximately 2 years. Similar to the report by Aldrich et al. [7], we also observed that age had an important impact on outcome. Children <1 year of age uniformly had a poor outcome, and the children <2 years of age had a relatively poor outcome compared to the older children. We found no difference in outcome between the older subgroups (ages ≥24 months). The similarity in outcome for infants and young children in our study and those of Aldrich et al. [7] help to validate and generalize the CBF and CO_2VR findings in this subgroup of patients in our current study.

Changes in CBF after TBI

There have been a few reports examining the changes in CBF after TBI in children. Kassoff et al. [11] reported on 10 children following severe TBI, 6 of whom had regional increases in CBF (2–5 times the normal gray matter flow) which were believed to represent hyperperfusion. Muizelaar et al. [5], also using the ^{133}Xe method, reported that lower values of CBF early after injury seemed to be related to a poor outcome. Sharples et al. [6], using the nitrous oxide method, also showed that mean CBF was higher in the good outcome group early after injury in children, and after 24 h, global CBF did not differ between outcome groups. Beyda [18], though, in a preliminary report using the ^{133}Xe method, found that initially low CBF values became hyperemic by the 3rd day after TBI, which he believed was secondary to the uncoupling of CBF and oxidative metabolism observed in adults [12, 15]. Also, since ICP peaked at this time, Beyda [18] suggested that there was a correlation between CBF and ICP. In our present study similar to Sharples et al. [6], CBF was initially significantly lower in the poor outcome group. By 24 h, there was no difference between good and poor outcomes. Any child with a global CBF of ≤20 ml/100 g/min at any point after TBI had a poor outcome. Early hypoperfusion after TBI observed in our study mirrors that seen in recent studies of adults after TBI [10, 16].

CBF and Hyperemia?

The relationship between post-traumatic 'hyperemia', diffuse cerebral swelling, and intracranial hypertension remains in question in children after severe TBI. Because children more commonly develop diffuse cerebral swelling than adults [7, 19, 20], it has been suggested since the initial pioneering work of Bruce et al. [4, 21] that the mechanism underlying this 'malignant' swelling was an age-related hyperemia. Brain swelling was previously believed to be due to 'vasomotor paralysis' and increased cerebral blood volume (CBV) and not edema [4]. Seminal

work by Marmarou et al. [22], using magnetic resonance imaging techniques in adults, suggests a heterogeneous response after TBI. Cytotoxic edema and reduced CBV occurred in the majority of adults during the initial 7 days after severe TBI, though normal and increased CBV occurred in a subset of patients who developed secondary cerebral swelling.

In studies performed during the delayed phase after TBI ($\geq$24 h), a high CBF (>55 ml/100 g/min) was significantly associated with a good outcome, and a CBF of >70 ml/100 g/min also tended to occur more often in the good outcome patients. Peak mean CBF was about 60 ml/100 g/min on days 1–2 after injury in our study. This is considerably greater than the peak CBF of about 45 ml/100 g/min in adults 23 h after severe TBI [20]. This may reflect either age-related differences in response to TBI, differences in methodology, or only age-related differences in normal CBF. Recently, Chiron et al. [23] using ^{133}Xe SPECT reported that CBF ranged from about 50 ml/100 g/min in normal neonates to 71 ml/100 g/min in 6–8 years olds, before declining to adult levels of 51 ml/100 g/min.

The most salient finding with respect to CBF measures $\geq$24 h after TBI in infants and young children is the heterogeneity between individual patients. For example, a CBF of 78 ml/100 g/min 48–72 h after injury in a 4-year-old child in our study with only mild hypoperfusion on admission, modest intracranial hypertension, intact CO_2VR and good outcome, almost certainly represents recovery of normal CBF. In contrast, a CBF of 58 ml/100 g/min 24 h after TBI in a 2-month-old infant in our study who presented with a CBF of only 9 ml/100 g/min on admission, had minimal CO_2VR, refractory intracranial hypertension and ultimately died, probably represents a marked hyperemic response. Whether the hyperemic response in this patient is coupled or uncoupled to metabolic demands, i.e., coupled to hyperglycolysis, was not addressed by our study; however, in this patient it represents a pathologic response temporally coupled to intracranial hypertension. These studies suggest that management decisions might be titrated to the underlying pathophysiology within a given child, at a specific time after injury, but clearly further serial studies are needed prior to any definitive protocols.

CO_2VR after TBI

In the landmark paper by Obrist et al. [12], normal CO_2VR was 3 $\pm$ 1% change in CBF/torr change in $PaCO_2$. Cold et al. [24] reported that CO_2VR was low (about 1.9%) after TBI when compared to normative data in adults. Enevoldsen and Jensen [14] reported that CO_2VR was lost following severe TBI, particularly in patients with severe injuries where they considered a value of $\leq$2% as abnormal. Some children as young as 6 years old were included but no separate analysis was performed. In this study in children, a CO_2VR of <2% was significantly associated with outcome since *all* patients with a poor outcome exhibited impaired global CO_2VR. Regional CO_2VR values, though, were quite variable between patients, often differed between hemispheres in a given patient, and only tended to be associated with outcome.

CBF values in most previous reports were normalized to a $PaCO_2$ of 34 mm Hg by assuming a CO_2VR of 3% [12, 14, 25, 26]. The validity of this technique for all trauma patients at all time points remains in question since prolonged hyperventilation may change CO_2VR [17, 25] and CO_2VR may be impaired. As seen in this study, there was significant variability of CO_2VR between and within outcome groups in the acute posttrauma period (<48 h) and, for that reason, CBF was not normalized to $PaCO_2$.

Limitations

Since this is a preliminary report, there are some limitations to the definitive conclusions that can be made. Despite the large number of CBF studies in this report, it must be noted that only 2 of the 10 patients with early low CBF ($\leq$20 ml/100 g/min) had a follow-up CBF study since many of the children with early low CBF died in the inital 24 h; both of the surviving children showed an up to 6-fold increase in CBF between the initial and later studies. As a result, additional serial studies beginning on admission and followed up at 24 and $\geq$48 h are needed in children <4 years of age. We have also noted in this study that a poor outcome was associated with early low CBF after TBI and young age, with the proportion of patients with a good outcome significantly increasing with age and higher CBF. However, the sample size in this preliminary study was limited, and it remains unclear from the data whether the low CBF observed was related to the low CBF values seen in normal infants and young children or to the mechanism of injury for this particular group, i.e., child abuse. Though the normal CBF is known to be lower in infants than older children, it is possible that low CBF after TBI caused or contributed to a poor outcome since infants may have less of a CBF reserve than older children. Since there is limited normative data for CBF in infants and young children, we can only definitively state that an early CBF of $\leq$20 ml/100 g/min is associated with a poor outcome, including infants and young children.

Conclusion

This preliminary study is the first report focusing on CBF in infants and young children after TBI. Infants and young children exhibiting low global CBF (≤ 20 ml/100 g/min) following severe TBI uniformly had a poor outcome. A CBF of >55 ml/100 g/min was associated with a significantly higher proportion of patients with a good outcome than with a poor outcome. This secondary increase in flow was probably multifactorial and could represent both recovery of normal CBF or a pathologic hyperemic response, depending on the individual case. CO_2VR was markedly impaired in infants and young children with a poor ultimate outcome. Although further studies are needed, it will be important to determine whether early low flow represents a therapeutic target in at least a subgroup of children. Finally, based on the variability of the pathophysiologic response, CBF-directed treatments should be titrated to the individual patient.

Acknowledgements

This work was supported in part by the Laerdal Foundation and the National Institute of Health (K08-NS01809-01) for Dr. Adelson. Dr. Kochanek was supported by an Established Investigator grant from the Society of Critical Care Medicine. The authors wish to thank Laura Biddle for manuscript preparation.

References

1 Luerssen TG, Klauber MR, Marshall LF: Outcome from head injury related to patient's age: A longitudinal prospective study of adult and pediatric head injury. J Neurosurg 1988;68: 409–416.

2 Ewing-Cobbs L, Miner ME, Fletcher JM, Levin HS: Intellectual, motor, and language sequelae following closed head injury in infants and preschoolers. J Pediatr Psychol 1989;14:531–547.

3 Levin HS, Eisenberg HM, Wigg NR, Kobayashi K: Memory and intellectual ability after head injury in children and adolescents. Neurosurgery 1982;11:668–673.

4 Bruce DA, Alavi A, Bilaniuk LT, Dolinskas C, Obrist W, Uzzell B: Diffuse cerebral swelling following head injuries in children: The syndrome of 'malignant brain edema'. J Neurosurg 1981;54:170–178.

5 Muizelaar JP, Marmarou A, DeSalles AAF, Ward JD, Zimmerman RS, Li Z, Choi SC, Young HF: Cerebral blood flow and metabolism in severely head-injured children. I: Relationship with GCS score, outcome, ICP, and PVI. J Neurosurg 1989a;71:63–71.

6 Sharples PM, Stuart AG, Matthews DSF, Aynsely-Green A, Eyre JA: Cerebral blood flow and metabolism in children with severe head injury. I: Relation to age, Glasgow coma score, outcome, intracranial pressure, and time after injury. J Neurol Neurosurg Psychiatry 1995a; 58:145–152.

7 Aldrich EF, Eisenberg HM, Saydjari C, Luerssen TG, Foulkes MA, Jane JA, Marshall LF, Marmarou A, Young HF: Diffuse brain swelling in severely head-injured children. A report from the NIH Traumatic Coma Data Bank. J Neurosurg 1992;76:450–454.

8 Kochanek PK, Clark RSB, Adelson PD, Marion DW: Severe traumatic brain injury in children: Pathobiology, management, and controversies; in Green TP, Weigle CGM (eds): Current Concepts in Pediatric Critical Care. Fullerton, Society of Critical Care Medicine, 1995.

9 Gur D, Yonas H, Good WF: Local cerebral blood flow by Xenon-Enhanced CT: Current status, potential improvements and future directions. Cerebrovasc Brain Metab Rev 1989; 1:68–86.

10 Marion DW, Darby J, Yonas H: Acute regional cerebral blood flow changes caused by severe head injuries. J Neurosurg 1991;74:407–414.

11 Kasoff SS, Zingesser LH, Shulman K: Compartmental abnormalities of regional cerebral blood flow in children with head trauma. J Neurosurg 1972;36:463–470.

12 Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA: CBF and metabolism in comatose patients with acute head injury. J Neurosurg 1984;61:241–253.

13 Jennett B, Bond M: Assessment of outcome after severe brain damage. Lancet 1985;i:480–484.

14 Enevoldsen EM, Jensen FT: Autoregulation and CO_2 responses of cerebral blood flow in patients with acute severe head injury. J Neurosurg 1978;48:689–703.

15 Obrist WD, Marion DW, Aggarwal S, Darby JM: Time course of cerebral blood flow and metabolism in comatose patients with acute head injury. J Cereb Blood Flow Metab 1993; 13(suppl):571.

16 Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF: Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. J Neurosurg 1992; 77:360–368.

17 Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF: Adverse effects of prolonged hyperventilation in patients with severe head injury: A randomized clinical trial. J Neurosurg 1991;75: 731–739.

18 Beyda DH: Time course of cerebral blood flow and metabolism in pediatric head trauma (abstract). Crit Care Med 1996;24:134.

19 Berger MS, Pitts LH, Lovely M, Edwards MS, Bartkowski HM: Outcome from severe head injury in children and adolescents. J Neurosurg 1985;62:194–199.

20 Zimmerman RA, Bilaniuk LT, Bruce D: Computed tomography of pediatric head trauma. Radiology 1978;126:403–408.

21 Bruce DA, Schut L, Bruno LA, Wood JH, Sutton LN: Outcome following severe head injuries in children. J Neurosurg 1978;48:679–688.

22 Marmarou A, Barzo P, Fatouros P, Yamamoto T, Doppenberg E, Muizelaar P, Bullock R, Young H: Traumatic brain swelling in head injured patients: Brain edema or vascular engorgement? Proc 10th Int Brain Edema Symp 1996, p 90.

23 Chiron C, Raynaud C, Maziere B, Zilbovicius M, Laflamme L, Masure M-C, Dulac O, Bourguignon M, Syrota A: Changes in regional cerebral blood flow during brain maturation in children and adolescents. J Nucl Med 1992;33: 696–703.

24 Cold GE, Jensen FT, Malmros R: The cerebrovascular CO_2 reactivity during the acute phase of brain injury. Acta Anaesthesiol Scand 1977; 21:222–231.

25 Muizelaar JP, Ward JD, Marmarou A, Newlon PG, Wachi A: Cerebral blood flow and metabolism in severely head-injured children. II: Autoregulation. J Neurosurg 1989;71:72–76.

26 Overgaard J, Tweed WA: Cerebral circulation after head injury. I: Cerebral blood flow and its regulation after closed head injury with emphasis on clinical correlations. J Neurosurg 1974; 41:531–541.