Cerebral autoregulation in pediatric traumatic brain injury*

Monica S. Vavilala, MD; Lorri A. Lee, MD; Krishna Boddu, MD, FANZCA; Elizabeth Visco, CRNA; David W. Newell, MD; Jerry J. Zimmerman, PhD, MD; Arthur M. Lam, MD, FRCPC

Objective: **The aims of this study were to document the incidence of impaired cerebral autoregulation in children with traumatic brain injury using transcranial Doppler ultrasonography and to examine the relationship between autoregulatory capacity and outcome in children following traumatic brain injury.**

Design: **Prospective cohort study.**

Setting: **Harborview Medical Center (level I pediatric trauma center) in Washington state.**

Patients: **Thirty-six children <15 yrs old with traumatic brain injury: Glasgow Coma Scale score <9 (n = 12, group 1), Glasgow Coma Scale score 9–12 (n = 12, group 2), and Glasgow Coma Scale score 13–15 (n = 12, group 3).**

Interventions: **Cerebral autoregulation testing was conducted during extracranial surgery. Mean middle cerebral artery flow velocities were measured using transcranial Doppler as mean arterial pressure was increased to whichever variable was greater: 20% above baseline or a set value (80 mm Hg for <9 yrs and 90 mm Hg for 9–14 yrs). Autoregulatory capacity was quantified by the Autoregulatory Index. Autoregulatory Index <0.4 was considered impaired cerebral autoregulation. Discharge outcome using the Glasgow Outcome Scale score was considered good if the Glasgow Outcome Scale score was ≥4.**

Measurements and Main Results: **Twenty-four (67%) of 36 children had an Autoregulatory Index ≥0.4. The incidence of impaired cerebral autoregulation was 42% (five of 12) in group 1, 42% (five of 12) in group 2, and 17% (two of 12) in group 3. Ten (42%) of the 24 children with intact cerebral autoregulation had a good outcome compared with only one of 12 (8%) children with impaired cerebral autoregulation ($p = .04$). Six of 12 (50%) children with impaired cerebral autoregulation had hyperemia compared with one of 24 (4%) children with intact cerebral autoregulation ($p < .01$). Hyperemia was associated with poor outcome ($p = .01$).**

Conclusions: **The incidence of impaired cerebral autoregulation was greatest following moderate to severe traumatic brain injury. Impaired cerebral autoregulation was associated with poor outcome. Hyperemia was associated with impaired cerebral autoregulation and poor outcome. (Pediatr Crit Care Med 2004; 5:257–263)**

KEY WORDS: cerebral autoregulation; pediatrics; head injury; outcome

Cerebral autoregulation refers to a homeostatic process whereby, in healthy adult patients, cerebral blood flow (CBF) remains constant between a mean arterial blood pressure (MAP) of 60 mm Hg and 160 mm Hg or between a cerebral perfusion pressure (CPP; MAP − intracranial pressure [ICP]) of 50 mm Hg and 150 mm Hg (1). In adults, there is evidence that autoregulation of CBF is impaired following traumatic brain injury (TBI) (2, 3). However, there is a paucity of information regarding the effect of TBI on cerebral autoregulation in children.

There are two published studies addressing cerebral autoregulation in children following TBI. Both investigations examined autoregulatory capacity in severe pediatric TBI. In 1989, Muizelaar et al. (4) examined cerebral autoregulation in 26 children with severe TBI using repeated xenon^{133} washouts. Changes in CBF in response to an increase in MAP with intravenous phenylephrine and a decrease in MAP using intravenous trimethaphan camsylate were measured. Cerebral autoregulation was defined as intact if %ΔCPP/%ΔCVR (cerebrovascular resistance) was ≤2. Autoregulatory capacity was found to be impaired in 15 of 37 (41%) of the measurements (4). However, unlike phenylephrine, trimethaphan has direct cerebral vasoconstrictive effects, a property that may make accurate determination of CBF and autoregulatory capacity unreliable (5). Six years later, Sharples et al. (6) published a study describing cerebral autoregulation in 17 children with ICP monitoring. These investigators used a modification of the Kety-Schmidt wash-in technique with 10% nitrous oxide as the tracer and jugular venous cannulation to calculate CBF and arteriovenous oxygen content difference. One hundred and twenty-two measurements of CVR were serially performed. CVR was calculated from CBF and CPP data according to the formula CVR = CPP/CBF, where CPP is calculated as MAP − ICP. CPP and CVR were correlated to describe cerebral autoregulation. The authors reported good correlation between CPP and CVR in subjects with good or moderate neurologic outcomes but no CPP and CVR correlation in subjects with poor outcome, suggesting impaired autoregulation in children with TBI and poor outcome. However, autoregulatory capacity was not quantified, and no information regarding the definition of intact vs. impaired autoregulation was provided (6). Although both Sharples et al. (6) and Muizelaar et al. (4) examined the relationship between autoregulatory capacity and outcome, results of the association are mixed. Furthermore, neither study provided direct estimates of the incidence

***See also p. 298.**

From the Departments of Anesthesiology (MSV, LAL, KB, EV, JJZ, AML), Pediatrics (MSV, JJZ), and Neurological Surgery (DWN, AML), University of Washington, Seattle, WA.

Supported, in part, by the American Heart Association Northwest Affiliate's Beginning Grant-in-Aid and by institutional and/or departmental sources.

DOI: 10.1097/01.PCC.0000123545.69133.C3

(percent of patients with impaired cerebral autoregulation) of impaired autoregulatory capacity following severe TBI.

The present study attempts to provide more information on the subject of cerebral autoregulation in pediatric TBI. The purpose of the present study is three-fold: a) to confirm earlier findings of impaired autoregulatory capacity using transcranial Doppler (TCD) ultrasonography in children with severe TBI; b) to document the incidence of impaired autoregulation in relation to the severity of TBI as defined by the Glasgow Coma Scale (GCS) score; and c) to describe the relationship between impaired cerebral autoregulation and outcome as defined by the Glasgow Outcome Scale (GOS) score.

MATERIALS AND METHODS

After institutional review board approval, written informed consent for participation in this study was obtained from parents of pediatric subjects. As invasive arterial pressure monitoring is required for cerebral autoregulation testing, only children with TBI requiring general anesthesia for extracranial surgery were enrolled over a period of 9 months. Perioperative monitoring of cerebral autoregulation was deemed beneficial by the attending anesthesiologist in the management of these children.

Experimental Protocol. General anesthesia was administered using a standardized premedication, induction, and maintenance regimen. In nonintubated patients, general anesthesia was induced with intravenous propofol 2 mg/kg and vecuronium 0.1 mg/kg. After tracheal intubation, anesthesia was maintained using low-dose sevoflurane (0.5–1.8%; <1 minimum alveolar concentration age-related end-tidal concentration) in 50% oxygen/50% air.

Invasive blood pressure with indwelling arterial catheters was used in all subjects. Blood pressure was recorded with the transducer at the level of the external auditory meatus (approximating the level of the circle of Willis). $Paco_2$ was measured from blood gas sampled during autoregulation testing to confirm end-tidal carbon dioxide. End-tidal carbon dioxide was monitored using a capnograph and maintained constant during testing. End-tidal sevoflurane concentration was maintained constant for a minimum of 15 mins before cerebral autoregulation testing began. Testing was conducted during steady-state surgical stimulation, as evidenced by unchanged mean middle cerebral artery flow velocities (Vmca) for ≥10 mins.

Determination of Middle Cerebral Artery Blood Flow Velocity and Definition of Absolute Hyperemia. All subjects were supine. In each participant, the middle cerebral arteries were insonated by TCD (Multidop X; DWL, Sipplingen, Germany) using standard protocols (7). Using a customized frame, the transducers were secured in place to ensure a constant angle of insonation (8). Bilateral Vmcas were averaged for analysis. For purposes of this study, absolute hyperemia was defined as Vmca >2 SD of the mean appropriate for age during similar anesthetic conditions (9).

Determination of Static Cerebral Autoregulation. During steady-state anesthesia, intravenous phenylephrine was titrated using a slow infusion (0.05–0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) over a 3- to 5-min period. Mean arterial pressure was increased according to whichever following variable was greater: a) 20% above baseline; or b) a set value of 80 mm Hg for the <9-yr age group and 90 mm Hg for the 9- to 14-yr age group. MAP and Vmca were simultaneously and continuously measured and recorded in the computer for subsequent off-line analysis.

Autoregulatory capacity was quantified with the Autoregulatory Index (ARI), which was calculated according to a previously published and commonly used formula (7). Mathematically, the ARI is the percent change in estimated cerebrovascular resistance (eCVR) per percent change in MAP (used when ICP was not measured) or CPP (used when ICP was measured

$$\text{ARI} = \%\Delta \text{ eCVR}/\%\ \Delta \text{ MAP or } \%\ \Delta \text{ CPP} \qquad [1]$$

The eCVR is the ratio of MAP to Vmca. Thus, an ARI of 0 represents absent autoregulation (pressure-dependent Vmca), whereas an ARI of 1.0 represents perfect autoregulation. To dichotomize the results for statistical analysis and in accordance with the previous definition of intact cerebral autoregulation, autoregulatory capacity was considered intact if the ARI was ≥0.4 (7).

In patients with ICP monitors, CPP was calculated as follows and used to calculate ARI:

$$\text{CPP} = \text{MAP} - \text{ICP} \qquad [2]$$

Definition of TBI, Determination of GCS Score, and Definition of GOS Score. For the purposes of this study, TBI was diagnosed if, before surgery, there was abnormal computed tomography (CT) of the head, history of loss of consciousness (level of consciousness), or abnormal mental status attributed to brain injury by the treating physician. The highest GCS score recorded in the medical record during the 24-hr period before surgery was used in the final analysis.

Outcome was evaluated using the GOS at the time of hospital discharge: GOS 1, death; GOS 2, vegetative state; GOS 3, alive but functionally impaired; GOS 4, minimal dysfunction; GOS 5, premorbid level of functioning. Poor outcome was defined as a GOS <4 and good outcome was defined as a GOS of 4 or 5 (10).

Statistical Analysis. To assess the influence of severity of TBI on autoregulatory capacity, patients were divided into three groups before cerebral autoregulation testing: group 1, GCS <9; group 2, GCS 9–12; and group 3, GCS 13–15. To determine the relationship between autoregulatory capacity and outcome, patients were divided into two groups: GOS <4 and GOS ≥4. In addition, each patient's ARI values and baseline Vmca were compared with previously published age-related ARI and Vmca values (at age appropriate blood pressure) for children without neurologic disease having surgery under similar anesthetic conditions (9). When baseline Vmca was >2 SD of the mean for the age group, absolute hyperemia was diagnosed. Fisher's exact test, Student's *t*-test, and analysis of variance were used as appropriate. Statistical significance was set at $p < .05$. All values are presented as mean ± SD.

Sample Size and Power Analysis. As the normal mean ARI in children without neurologic disease during similar anesthetic conditions is 0.75–1.0 (9), and a value of ≥0.4 is generally consistent with preserved cerebral autoregulation (11), a small difference in ARI would be clinically meaningless. Consequently, we considered a 30% difference in mean ARI to be significant. Assuming $p < .05$, $\alpha = .05$, and $\beta = .8$, power analysis indicated that we needed 12 subjects in each group for a total of 36 subjects.

RESULTS

Demographics. Thirty-six children (26 males and ten females aged 4 months to 14 yrs) with TBI were enrolled in the study. There were 12 subjects in each group: GCS <9 (group 1), GCS 9–12 (group 2), and GCS 10–13 (group 3). There was no difference in age between the groups (Table 1). All patients had a head CT on hospital admission. Mechanisms of injury included motor vehicle crash (57%), fall (27%), car vs. pedestrian (6%), and other (10%).

Only one child had inflicted TBI. All children with moderate (n = 12) to severe (n = 12) TBI had diffuse brain injury by head CT: diffuse axonal injury (n = 16), cerebral edema (n = 13). There were three cases of focal brain injuries superimposed on diffuse TBI: two subdural hematomas and one epidural hematoma. Of the 12 children with mild TBI, eight had loss of consciousness at the scene and symptoms of concussion but no CT evidence of brain injury; the remaining four children had contusions (n = 1), epidural hematoma (n = 1), subdural hematoma (n = 1), and skull fractures (n = 1). The mean overall Injury Severity Score was 25 ± 20. Injury Severity Scores were 1 ± 3 (GCS 13–15), 9 ± 5, (GCS 9–12), and 30 ± 12 (GCS <9) for mild, moderate,

and severe TBI, respectively. The type of injuries that warranted surgical intervention included femur fractures (n = 15), lower extremity lacerations (n = 2), pelvic fractures (n = 3), humerus fractures (n = 2), hollow viscus injuries (n = 8), suspected abdominal injury (n = 3), and orbital fractures (n = 3). All patients with moderate to severe TBI received sedation and analgesia with intravenous infusions of lorazepam and morphine during transport to the operating room compared with children with mild TBI, who received intravenous morphine via either patient-controlled analgesia, intermittent blouses, or continuous infusions.

Bilateral TCD measurements were obtained in all children. The mean GCS of all 36 patients was 11 ± 4 and the mean $Paco_2$ was 35.6 ± 2.2 mm Hg. On average, cerebral autoregulation testing was performed on postinjury day 9.6 ± 16 (range, 0–36; Fig. 1). Children with severe TBI had surgery later after initial insult compared with children with moderate or mild TBI (severe 9.4 ± 13.0 vs. moderate 5.4 ± 5.6 vs. mild 3.5 ± 3.7, p = .04; Table 1). The average duration of surgery was 2.4 hrs. Preoperative hematocrit was available in all children (30 ± 4%). All patients maintained normal temperature (35.5–37.1°C) during testing. Eleven (29%) of 36 children had indwelling ICP monitors during cerebral autoregulation testing. One child, 2 yrs of age, died on hospital day 2. All 12 of the children with severe TBI and seven of 12 of the children with moderate TBI arrived to the operating room with tracheal tube *in situ* and receiving mechanical ventilation.

Cerebral Autoregulation. Overall ARI of all 36 subjects was 0.61 ± 0.37 (range, 0–1). The mean ARI for groups 1, 2, and 3 was 0.47 ± 0.41, 0.52 ± 0.42, and 0.68 ± 0.38, respectively (range, 0–1). There was no significant difference in ARI between the groups (p = .72; Table 1) or in ARI between hemispheres in the four patients with mild focal TBI (ARI 0.66 ± 0.3 vs. 0.69 ± 0.4).

Autoregulation was impaired in 12 of 36 (33%) children. The mean ARI was 0.26 ± 0.13 (range, 0–0.26). There was a trend toward increased risk of impaired cerebral autoregulation in children with moderate (42%; five of 12) to severe (42%; five of 12) TBI compared with children with mild (17%; two of 12) injury, but the difference in incidence between these groups was not statistically significant (p = .18). There was no difference in either age (p = .21) or GCS (p = .16) between the impaired and intact groups. None of the eight children who underwent cerebral autoregulation testing beyond postinjury day 8 had impaired autoregulatory capacity. Four of the 12 patients with impaired autoregulatory capacity had an ARI of 0.

Seven of 36 (20%) patients had absolute hyperemia (9, 12). Six of the seven patients with hyperemia had impaired cerebral autoregulation (ARI, 0.11 ± 0.17; range, 0–0.39; GOS, 2.3 ± 1.2). Among patients without hyperemia and intact cerebral autoregulation, Vmca was significantly lower than normal for age/anesthetic conditions in all four age groups (10, p < .01, Fig. 2). Six (50%) of the 12 children with TBI and impaired cerebral autoregulation had hyperemia compared with one of 24 (4%) children with TBI and intact cerebral autoregulation (p < .01; positive predictive value, 0.86; 95% confidence interval, 0.46–0.99). The one child with hyperemia and intact cerebral autoregulation was a 2-yr-old suffering from nonaccidental trauma-related TBI with an ARI of 0.5.

The overall discharge GOS score was 3.1 ± 0.9 (range, 0–5); 13 children had a good outcome (GOS ≥4) and 23 children had a poor outcome (GOS <4). Ten of 12 (83%) children with mild TBI had a good outcome compared with three of 12 (36%) children with moderate or zero of 12 (0%) children with severe TBI (group 3 GOS 3.9 ± 0.6 vs. group 2 GOS 3.0 ± 0.41 vs. group 1 GOS 2.2 ± 0.4; p < .001). Ten of the 24 (42%) children with intact cerebral autoregulation had a good outcome compared with only one of 12 (8%) children with impaired cerebral autoregulation (p = .04, Table 2). Although there was no difference in GOS between children with intact vs. impaired cerebral autoregulation (2.7 ± 0.6 vs. 3.2 ± 0.9, p = .24), children with a good outcome tended to have higher ARI values compared with children with a poor outcome (0.78 ± 0.32 vs. 0.52 ± 0.37, p = .07). Three of the four patients with an ARI of 0 had a poor outcome. The one patient in this study who died had an ARI of 0 (tested postinjury day 2). Outcome in children with TBI and hyperemia was poor compared with children with TBI and no hyperemia (GOS 2.5 ± 1.2 vs. GOS 3.9 ± 0.9, p = .01; positive predictive value, 0.92; 95% confidence interval, 0.66–0.99). The one patient with hyperemia and intact cerebral autoregulation (ARI 0.5) also had a poor outcome.

Table 1. Incidence of impaired cerebral autoregulation in mild, moderate, and severe traumatic brain injury

All Subjects	Group I (GCS <9) (n = 12)	Group 2 GCS 9–12 (n = 12)	Group 3 GCS 13–15 (n = 12)	p
Age, yrs	7.8 ± 3.6	13.0 ± 4.5	8.8 ± 5.6	.09
Mean GCS	6.3 ± 2.3	10.8 ± 1.3	14.0 ± 1.0	—
PID, days	9.4 ± 13.0	5.4 ± 5.6	3.5 ± 3.7	.04
Mean ARI	0.47 ± 0.41	0.52 ± 0.42	0.68 ± 0.38	.72
No. impaired (%)	5/12 (42)	5/12 (42)	2/12 (17)	.18
GOS	2.2 ± 0.4	3.0 ± 0.41	3.9 ± 0.6 vs.	<.001

GCS, Glasgow Coma Scale; PID, postinjury day; ARI, Autoregulatory Index; GOS, Glasgow Outcome Scale. All values are expressed as mean ± SD unless otherwise stated.

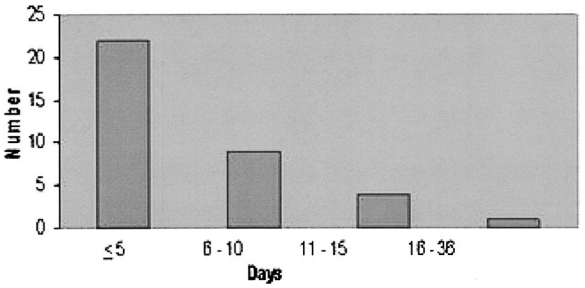

Figure 1. Time of cerebral autoregulation testing following traumatic brain injury (TBI): on average, cerebral autoregulation testing was performed on postinjury day 9.6 ± 16 (range, 0–36). Most children had autoregulation testing during the first 5 days following TBI.

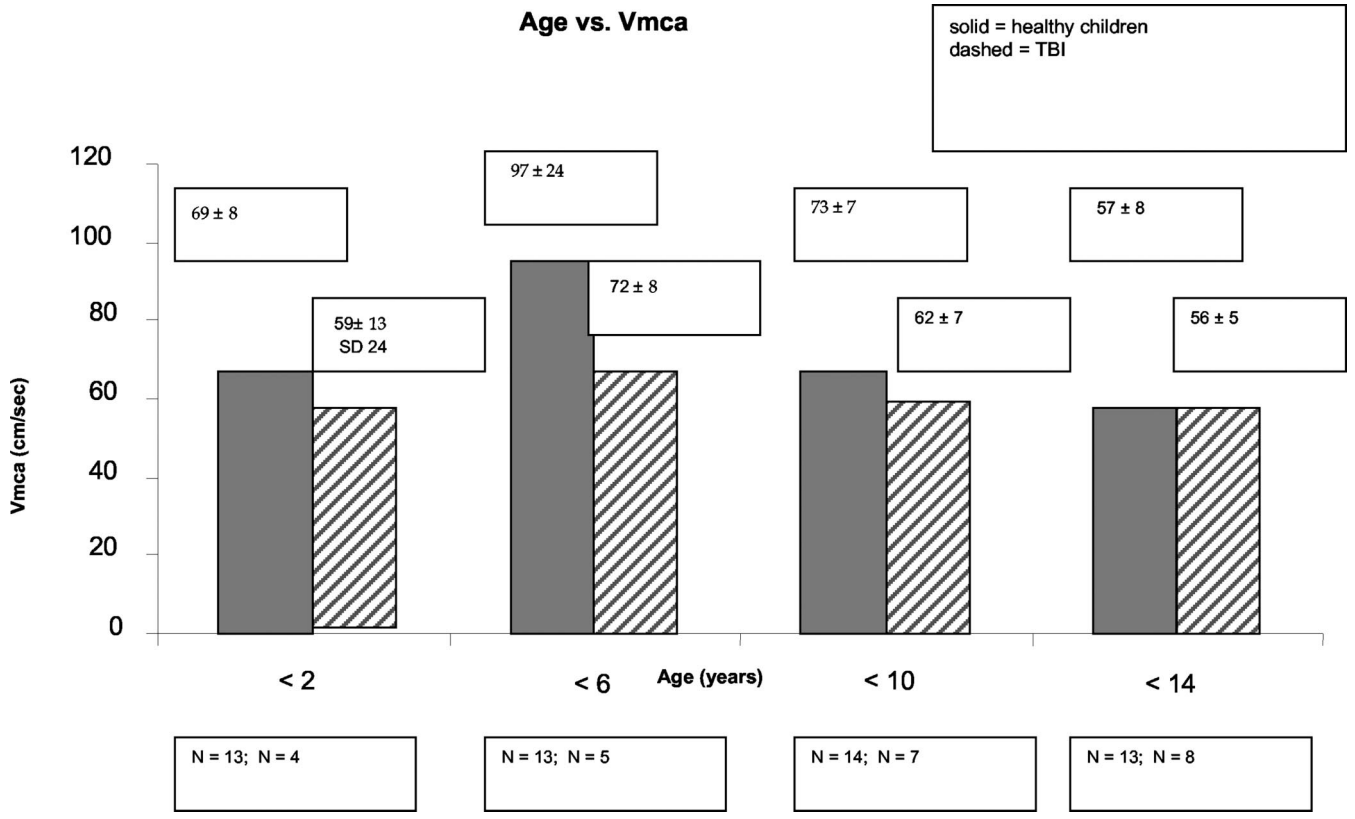

Figure 2. Age-related mean middle cerebral artery flow velocities (*Vmca*) in children with intact cerebral autoregulation: with traumatic brain injury (*TBI*) (n = 24) and historical controls without TBI (10; n = 53). Vmca is decreased for age in all age groups compared with historical controls ($p < .01$) during similar anesthetic conditions. Data are presented as mean ± SD.

DISCUSSION

The main findings in this study are that a) cerebral autoregulation may be impaired following mild, moderate, and severe pediatric TBI; b) hyperemia was associated with impaired cerebral autoregulation; and c) impaired cerebral autoregulation was associated with poor outcome. To the best of our knowledge, this is the first examination of cerebral autoregulation in children with varying severity of TBI using a bedside, noninvasive technology (TCD).

In adults, impaired cerebral autoregulation has been described following mild and severe TBI (2,3). Using dynamic autoregulation testing methodology, which measures the rate of return of Vmca to baseline following a transient decrease in MAP, Junger et al. (2) reported a 28% incidence of impaired cerebral autoregulation in patients with mild TBI. Using static autoregulation testing methodology in adults with severe TBI, Sahuquillo et al. (3) reported impaired or abolished autoregulation in 21 of 31 (67%) patients. The incidence of impaired cerebral autoregulation in pediatric TBI has been difficult to estimate because Muizelaar et al. (4) reported their estimates of impaired autoregulation in terms of number of measurements and not in terms of impairment per number of subjects. Although Sharples et al. (6) correlated impaired cerebral autoregulation with severity of TBI, the lack of direct cerebral autoregulation testing and the absence of definition of intact vs. impaired autoregulation make estimating the incidence of impaired autoregulation problematic. In this regard, the present study, which evaluated autoregulatory capacity using TCD, provides the first true estimates of the incidence of impaired autoregulation with varying degrees of TBI. Our data indicate that, similar to adults, children with more severe TBI have a higher incidence of impaired cerebral autoregulation.

Given our present findings, the clinical implications of impaired autoregulation merit discussion. Impaired cerebral autoregulation means that CBF is dependent on MAP or CPP. Therefore, even small decreases in CPP at a time when cerebral autoregulation is impaired may

Table 2. Autoregulatory index (ARI), postinjury day (PID), and age

	ARI <0.4 (n = 12)	ARI ≥0.4 (n = 24)	*p*
Age, yrs	11.4 ± 4.8	9.3 ± 4.4	.21
GCS	9.9 ± 4.0	10.5 ± 3.7	.16
No. with hyperemia (%)	6/12 (50)	1/24 (4)	<.01
PID, days	2.4 ± 2.8	4.8 ± 5.1	.21
GOS <4	10/12 (83%)	2/12 (17%)	.04
GOS	2.7 ± 0.6	3.2 ± 0.9	.24

ARI ≥0.4 and ARI <0.4 refer to intact and impaired cerebral autoregulation respectively. There was no relationship between impaired autoregulation and age or GCS. Impaired autoregulation was associated with hyperemia and poor outcome.

theoretically increase the risk of cerebral ischemia. If hypotension occurs in the course of blood pressure fluctuations during surgery, these patients may be at risk of secondary neurologic injury. Conversely, small increases in blood pressure may result in hyperemia and increase the risk of intracranial hemorrhage. Consequently, maintaining "tight control" of MAP or CPP during general anesthesia and in the intensive care unit may be even more important in children with impaired cerebral autoregulation (13).

The relationship between autoregulatory capacity and outcome following TBI is intriguing, multifactorial, and potentially complex. Loss of autoregulation with poor outcome may reflect the severity of TBI in patients with impaired autoregulation. On the other hand, impaired cerebral autoregulation may affect outcome. Not surprisingly, published reports of the relationship between autoregulatory status and ultimate outcome are mixed (3, 4, 6, 14–16). In the present study, we did not find a significant difference in mean GOS score between children with impaired vs. intact cerebral autoregulation. However, children with impaired cerebral autoregulation had a greater proportion of poor discharge outcomes compared with children with intact cerebral autoregulation. This is consistent with results reported by Lam et al. (14) in adults, where all five patients with intact autoregulation had good outcome, whereas the 11 patients with permanent loss of autoregulation either died or were severely disabled. Given the potential variability of autoregulatory capacity with time, it is conceivable that a simple relationship between autoregulatory capacity and outcome does not exist. This is a potential confounder. For example, Czosnyka et al. (15, 16) reported disturbed autoregulation during the first 2 days in patients who died following TBI. Outcome was much more variable in those with transient loss of autoregulation; 40% of these patients had a good outcome and 60% had a poor outcome. The factors that contributed to poor outcome in those with transient loss of autoregulatory capacity were not clearly identified. The sample size in the present preliminary study is too small to account for all confounders. However, it is possible that hypotension in patients with impaired autoregulation is one of those factors. We speculate that autoregulatory status may be an important outcome modifier following TBI if hemodynamic instability exists. Since we tested autoregulation only once in each patient, we were unable to identify which patients had transient vs. permanent impairment of autoregulation. However, despite the observation in this series that the ARI was always preserved when tested beyond postinjury day 8, there was no significant difference in the elapsed time before testing between patients with intact vs. impaired cerebral autoregulation. The majority of the patients had autoregulation testing done during the first 5 days following TBI, as this represents the window when the patients were considered stable for surgery.

Hyperemia has been reported to be a distinguishing feature of pediatric TBI (17, 18), but this conventional wisdom has recently been challenged (19, 20). It is unclear, in studies reporting hyperemia, whether reported CBF values were compared with age-matched controls or adult CBF values. If adult CBF values were used, then children with age-appropriate but higher Vmca values, compared with adults, would be falsely diagnosed with hyperemia. Furthermore, radiographic studies have found no correlation between CBV and CBF or between CBV and brain swelling using xenon-enhanced CT (19). Bouma et al. (19) argued that although increased CBV may contribute to increased ICP, brain swelling is not caused by increased CBV alone. Sharples et al. (6) did not comment on the incidence of hyperemia in their subjects, and it is unclear whether Muizelaar et al. (4, 17) compared CBF values in children to normal values for adults, raising doubts about estimates of the incidence of hyperemia in pediatric TBI. In the present study, <25% of children with TBI had absolute hyperemia (9,12). Compared with age-matched historical controls during similar anesthetic conditions, Vmca was decreased for age in children with intact autoregulatory capacity (9). This pattern is consistent with adult data and probably reflects decreased cerebral metabolic rate following TBI (4). Finally, similar to Sharples et al. (6), we present Vmca data uncorrected for $Paco_2$. Although this theoretically underestimates the incidence of absolute hyperemia, we found no difference in the incidence of hyperemia when we corrected Vmca to $Paco_2$ 37.1 (mean end-tidal carbon dioxide in historical controls during similar anesthetic conditions) assuming an overall change of 3% in CBF for every mm Hg change in $Paco_2$. The difference in Vmca between the current subjects with intact cerebral autoregulation and historical controls (9) remained significant for all age groups. Since it is unclear how CO_2 reactivity is altered in pediatric TBI, thereby making any empirical adjustment of Vmca for $Paco_2$ unreliable, we report our Vmca data uncorrected for $Paco_2$ (35.6 ± 2.2 mm Hg).

In the present study, we found an association between hyperemia and impaired cerebral autoregulation. A similar loss of autoregulation was reported by McCulloch et al. (21) in adults. This finding is not surprising since hyperemia suggests a decrease in basal vascular tone and, hence, an inability to respond to a change in blood pressure. Alternatively, in patients with impaired cerebral autoregulation, Vmca will vary directly with blood pressure and hyperemia will occur with hypertension. This association between hyperemia and impaired autoregulatory capacity may have management and prognostic implications for the subset of children with hyperemia following TBI.

There are some limitations to our study. Foremost, the use of TCD ultrasonography to estimate CBF merits discussion. TCD ultrasonography measures Vmca and not CBF in the vessel examined. Hence, TCD ultrasonography is not the gold standard for measuring CBF. However, TCD ultrasonography is considered to be an appropriate surrogate for studying CBF since changes in flow velocity are proportional to changes in flow (22). This is premised on the fact that the diameter of the conductance vessel stays constant, and this has been shown to be the case with cerebral vasoconstriction and vasodilation (23). Vasospasm is the only pathologic condition that primarily affects the diameter of the middle cerebral artery (conductance vessel). However, vasospasm does not occur unless the patient has suffered subarachnoid hemorrhage, and in adults it has been reported to occur in 20% of patients with traumatic subarachnoid hemorrhage (24). There are few studies describing the incidence of vasospasm in children with head injuries. Although there is no standard definition for hyperemia in children, normal Vmca values are known and hyperemia appears to be more common in children with TBI than vasospasm. In a recent study of 27 children with head injuries, including seven with subarachnoid hemorrhage, Mandera et al. (25) reported that all high flow velocities were due to hyperemia and not vasospasm.

Children with traumatic brain injury have impaired cerebral autoregulation, and this impairment occurs in moderate to severe as well as mild injury.

Only four children in the present study, and none in the impaired group, had subarachnoid hemorrhage, making it highly unlikely that the seven patients with increased Vmcas in the present study were due to vasospasm and not hyperemia. Although theoretically, compression of middle cerebral artery can occur with very high ICP, leading to an increase in flow velocity while flow actually decreases (as in vasospasm), in reality this does not occur. As ICP increases, vascular resistance increases primarily because of compression of the distal resistance vessels. The progression and change in flow velocity pattern with increasing ICP have been well characterized (26). Increased ICP results in an initial decrease in diastolic flow velocity followed by an oscillating flow pattern (intracranial circulatory arrest) and eventually disappearance of TCD signal. This pattern was not observed in any of our patients; thus, neither vasospasm nor increased ICP was a confounding factor in this study.

Although both the Kety-Schmidt and CT-xenon^{133} techniques directly measure CBF, they are invasive and cannot be performed at the bedside. Although TCD is not a direct method and indirectly measures only global CBF, its relatively noninvasive nature makes it suitable as a bedside measurement and perhaps makes it a more clinically applicable test. Finally, interoperator variability is low with TCD when the operators are experienced in use of the technology (27, 28). In this study, all TCD measurements were performed by the same investigator, who was experienced in the use of TCD.

As we only examined children when they presented for surgery, we could not control for the time of testing. Although it would be ideal to repeatedly test these children in the intensive care unit immediately following injury, this poses logistical difficulties and would necessitate invasive arterial pressure monitoring for a long period of time. Understanding the time course of change in autoregulation may be important because the period during transient loss of autoregulation may represent a critical stage following initial neurologic insult where a subset of patients may be at risk of secondary TBI. However, it was not the purpose of our study to describe the time course of return of autoregulation in individual children. The trend in our data, however, suggests that autoregulatory capacity changes over time and, in some cases, may return to normal soon after TBI (14). Similarly, our hypothesis that Vmca may be decreased for some time after initial injury is based on cross-sectional data as patients were not serially tested. Although logistically difficult, a future study using serial testing of autoregulatory capacity is warranted. Although it may be ideal to test cerebral autoregulation without the influence of a general anesthetic to exclude a sevoflurane effect on Vmca, the dose of sevoflurane used in the present study has been shown to have little effect on Vmca or cerebral autoregulation (29–33). ICP is not reported in this study because only 11 of 36 children had indwelling ICP monitors, and only one of 11 patients had ICP measurements >20 mm Hg (22 mm Hg) during autoregulation testing. In other patients, ICP monitoring either was not indicated (mild to moderate head injury) or was removed before presenting for surgery because intracranial hypertension had resolved.

Finally, outcome was examined only at hospital discharge and not thereafter. Although it would have been ideal to use GOS at 6 months or 1 yr and outcome tools describing functions of daily living or school performance, we used the GOS score in this study because, as an outcome measure, it may more closely reflect the proximate effects of the physiologic testing of cerebral autoregulation. Although we cannot compare the relative importance of loss of cerebral autoregulation and poor outcome to other clinical predictors, because of small sample size, this report provides important physiologic observations about the association between impaired cerebral autoregulation and poor outcome. In future studies using serial testing of cerebral autoregulation, follow-up GOS at 1 yr would be more appropriate (34).

CONCLUSIONS

Children with TBI have impaired cerebral autoregulation, and this impairment occurs in moderate to severe as well as mild injury. Impaired autoregulatory capacity may be associated with poor discharge outcome. Although not as common as previously thought, hyperemia appears to be associated with impaired cerebral autoregulation and poor outcome. These findings may have implications for clinicians managing children with TBI. Further studies characterizing cerebral autoregulation in pediatric TBI are needed to understand the role of autoregulatory capacity in determining outcome.

REFERENCES

1. Paulson OB, Strandgaard S, Edvinson L: Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; 2:161–191
2. Junger EC, Newell DW, Grant GA, et al: Cerebral autoregulation following minor head injury. *J Neurosurg* 1997; 86:425–432
3. Sahuquillo J, Munar F, Baguena M, et al: Evaluation of CO_2 reactivity and autoregulation in patients with post-traumatic diffuse brain swelling (diffuse injury III). *Acta Neurochir Suppl (Wien)* 1998; 71:233–236
4. Muizelaar JP, Marmarou A, DeSalles AA, et al: Cerebral blood flow and metabolism in severely head injured children. Part 2: Autoregulation. *J Neurosurg* 1989; 71:72–76
5. Stoyka WW, Schutz HH: The cerebral response to sodium nitroprusside and trimethaphan controlled hypotension. *J Can Anesth Soc* 1975; 22:275–283
6. Sharples PM, Matthews DSF, Eyre JA: Cerebral blood flow and metabolism in children with severe head injuries. Part 2: Cerebrovascular resistance and its determinants. *J Neurol Neurosurg Psychiatry* 1995; 58:153–159
7. Strebel S, Lam AM, Matta B, et al: Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *Anesthesiology* 1995; 83:66–76
8. Lam AM: Intraoperative transcranial Doppler monitoring. *Anesthesiology* 1995; 82: 1536–1537
9. Vavilala MS, Lee M, Lee LA, et al: Cerebral autoregulation in healthy children during sevoflurane anesthesia. *Br J Anaesth* 2003; 90:636–641
10. Jennett B, Bond MR: Assessment of outcome after severe brain damage: A practical scale. *Lancet* 1975; 1:480–485
11. Tiecks FP, Lam AM, Aaslid R, et al: Comparison of static and dynamic cerebral autoregulation measurements. *Stroke* 1995; 1014–1019
12. Bode H: Pediatric Application of Transcranial Doppler Ultrasonography. New York, Springer-Verlag, 1988

13. Guidelines for the management of severe head injury. Brain Trauma Foundation, American Association of Neurological Surgeons, Joint Section on Neurotrauma and Critical Care. *J Neurotrauma* 1996; 13: 641–734
14. Lam JM, Hsiang JN, Poon WS: Monitoring of autoregulation using laser Doppler flowmetry in patients with head injury. *J Neurosurg* 1997; 86:438–445
15. Czosnyka M, Smielewski P, Piechnik S, et al: Continuous monitoring of cerebrovascular pressure-reactivity in head injury. *Acta Neurochir Suppl* 2000; 76:483–484
16. Czosnyka M, Smielewski P, Kirkpatrick P, et al: Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996; 27: 1829–1834
17. Muizelaar JP, Marmarou A, DeSalles AA, et al: Cerebral blood flow and metabolism in severely head injured children. Part 1: Relationship with GCS score, outcome, ICP and PVI. *J Neurosurg* 1989; 71:63–71
18. Bruce DA: Diffuse cerebral swelling following head injuries in children: The syndrome of "malignant brain" edema. *J Neurosurg* 1997; 54:170–178
19. Bouma GJ, Muizelaar JP, Fatouros P: Pathogenesis of traumatic brain swelling: Role of cerebral blood volume. *Acta Neurochir Suppl (Wein)* 1998; 71:272–275
20. Zwinenberg M, Muizelaar JP: Severe pediatric head injury: The role of hyperemia revisited. *J Neurotrauma* 1999; 16:937–943
21. McCulloch TJ, Visco E, Lam AM: Graded hypercapnia and cerebral autoregulation during sevoflurane or propofol anesthesia. *Anesthesiology* 2000; 93:1205–1209
22. Larsen FS, Olsen KS, Hansen BA, et al: Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994; 25:1985–1988
23. Giller CA, Hatab MR, Giller AM: Estimation of vessel flow and diameter during cerebral vasospasm using transcranial Doppler indices. *Neurosurgery* 1998; 42:1076–1081
24. Martin NA, Doberstein C, Alexander M, et al: Posttraumatic cerebral arterial spasm. *J Neurotrauma* 1995; 12:897–901
25. Mandera M, Larysz D, Wojtacha M: Changes in cerebral hemodynamics assessed by transcranial Doppler ultrasonography in children after head injury. *Childs Nerv Syst* 2002; 18:124–128
26. Hassler W, Steinmetz H, Gawlowski J: Transcranial Doppler ultrasonography in raised intracranial pressure and in intracranial circulatory arrest. *J Neurosurg* 1988; 68:745–751
27. Minciotti P, Ceravolo MG, Provinciali L: Inter-examiner variability of transcranial Doppler procedure and reports: a multicenter survey. Italian Transcranial Doppler Group. *Ital J Neurol Sci* 1997; 18:21–30
28. Shen Q, Stuart J, Venkatesh B, et al: Inter observer variability of the transcranial Doppler ultrasound technique: impact of lack of practice on the accuracy of measurement. *J Clin Monit Comput* 1999; 15:179–184
29. Lu H, Werner C, Engelhard K, et al: The effects of sevoflurane on cerebral blood flow autoregulation in rats. *Anesth Analg* 1998; 87:854–858
30. Fischer AQ, Truemper EJ: Transcranial Doppler applications in the neonate and child. *In:* Transcranial Doppler Ultrasonography. Babikian VL, Wechsler LR (Eds). St. Louis, MO, Mosby, 1993, pp 282–302
31. Bedforth NM, Hardman JG, Nathanson MH: Cerebral hemodynamic response to the introduction of desflurane: A comparison with sevoflurane. *Anesth Analg* 2000; 91:152–155
32. Endoh H, Honda T, Ohashi S, et al: Cerebral autoregulation during sevoflurane or isoflurane anesthesia: Evaluation with transient hyperemic response. *Masui* 2001; 50: 1316–1321
33. Summors AC, Gupta AK, Matta BF: Dynamic cerebral autoregulation during sevoflurane anesthesia: A comparison with isoflurane. *Anesth Analg* 1999; 88:341–345
34. Jennett B, Bond MR: Assessment of outcome after severe brain damage: A practical scale. *Lancet* 1975; 1:480–484