

Young Age as a Risk Factor for Impaired Cerebral Autoregulation after Moderate to Severe Pediatric Traumatic Brain Injury

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Background: Little is known about age and cerebral autoregulation in children with traumatic brain injury (TBI). The authors compared cerebral autoregulation between young (aged <4 yr) and older (aged ≥4 yr) children with TBI.

Methods: After University of Washington's institutional review board approval, a retrospective analysis of prospectively collected data (May 2002 and June 2007) was performed. Eligibility criteria included age 16 yr or younger, moderate to severe (admission Glasgow Coma Scale score <13) TBI, TBI on computed tomography scan, and tracheal intubation. Cerebral autoregulation testing was performed within 72 h after TBI, and autoregulation was quantified using the autoregulatory index. An autoregulatory index less than 0.4 represents impaired cerebral autoregulation. The 12-month Glasgow outcome score was measured. Data are presented as mean ± SD or range.

Results: Thirty-seven children (8.9 ± 5.1 yr; 0.8–16 yr) were enrolled. Children younger than 4 yr had a higher incidence of impaired cerebral autoregulation (8 of 10 vs. 7 of 27; $P = 0.006$) and worse 12-month outcome (Glasgow outcome score 3.0 ± 1.0 vs. 4.0 ± 1.0 ; $P = 0.02$) than older children. Age less than 4 yr (adjusted odds ratio, 12.2; 95% confidence interval, 1.5–98.5) and low Glasgow Coma Scale score (adjusted odds ratio for higher Glasgow Coma Scale, 0.53; 95% confidence interval, 0.30–0.96) were independently associated with impaired cerebral autoregulation.

Conclusions: Age less than 4 yr was a risk factor for impaired cerebral autoregulation, independent of TBI severity. Age-related factors may play a role in the mechanisms maintaining or worsening cerebral autoregulation in children after TBI.

CEREBRAL autoregulation is a dynamic process whereby arteriolar diameter increases and decreases to preserve normal cerebral blood flow (CBF).¹ Disease states, including trauma, may damage this homeostatic autoregulatory process.^{2,3} Loss of cerebral autoregulation after

traumatic brain injury (TBI) may contribute to cerebral ischemia and/or cerebral hyperemia and may worsen outcome.^{2,4–6} Although the worst outcomes after TBI occur in children younger than 4 yr,⁷ there is no information regarding the relation between age and cerebral autoregulation after pediatric TBI.

The incidence of impaired cerebral autoregulation in adults with severe TBI approaches 70%.² In 1989, Muijelaar *et al.*⁸ provided the first report of impaired cerebral autoregulation in 40% of children with severe TBI. In 1995, Sharples *et al.*⁹ described a correlation between loss of cerebral perfusion pressure (CPP) and cerebrovascular resistance with poor outcome in 17 children with severe TBI. In a slightly larger series, Vavilala *et al.*⁴ reported 42% impaired cerebral autoregulation in 36 children with moderate and severe TBI. These studies suggest that children are at risk for secondary injury from loss of autoregulation after TBI. However, none of these studies described age-related differences in cerebral autoregulation. This is relevant because impaired cerebral autoregulation after pediatric TBI has been associated with poor 6-month outcome,⁴ but the relation between age, impaired cerebral autoregulation, and outcome has not been examined. Given that animal studies show age-related differences in cerebral autoregulation after fluid percussion injury,¹⁰ the effect of age on cerebral autoregulation after pediatric TBI may be important. Therefore, we hypothesized that young children with moderate and severe TBI have a higher incidence of impaired cerebral autoregulation than older children with comparable TBI severity.

Materials and Methods

After institutional approval from the University of Washington (Seattle, Washington) Human Subjects Review Committee, we performed a retrospective analysis of prospectively collected data from an ongoing larger observational cohort study examining cerebral autoregulation after pediatric TBI at Harborview Medical Center (level 1 pediatric trauma center) over a 5-yr period (May 2002 through June 2007). Consent was obtained from parents or legal guardians.

Study Participants

Eligibility criteria for the prospective study included age 16 yr or younger, admission to the Harborview Medical Center pediatric intensive care unit with a diag-

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Received from the Departments of Anesthesiology, Pediatrics, and Neurological Surgery, University of Washington, Seattle, Washington; and the Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania. Submitted for publication July 23, 2007. Accepted for publication December 10, 2007. Supported in part by American Pediatric Society and Society for Pediatric Research National Institutes of Health grant No. T35-HD007446 (to S. Freeman) and National Institutes of Health grant No. K23-HD044632 (to Dr. Vavilala), Bethesda, Maryland. None of the authors have financial interest in this research.

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nosis of moderate to severe TBI (admission Glasgow Coma Scale [GCS] score <13), TBI on computed tomography (*i.e.*, subdural hematoma) scan, and tracheal intubation. Children with extracranial injuries were included. We excluded children with isolated focal TBI such as epidural or subdural hematoma, hemodynamic instability (per treating intensivist if significant hypotension or hypertension was present immediately before testing), or patients with no available parent or guardian at the time of enrollment. We reviewed medical records for eligibility, relevant medical history, and physiologic data. Study participants underwent cerebral autoregulation testing if they were considered hemodynamically stable by the treating pediatric intensivist. Cerebral autoregulation was examined at the patient's bedside in the pediatric intensive care unit. The research nurse, who was trained in GCS scoring and not involved in determining middle cerebral artery flow velocity (V_{mca}), autoregulatory index (ARI), or 12-month Glasgow outcome score (GOS), determined GCS score at the time of cerebral autoregulation testing. Temperature was measured *via* the tympanic route in all patients by the treating bedside nurse as per pediatric intensive care unit protocol.

Measuring Middle Cerebral Artery Blood Flow Velocity

Transcranial Doppler ultrasonography (Multidop X; DWL Corp., Sipplingen, Germany) was used to measure bilateral flow velocities in the middle cerebral artery using a 2-MHz ultrasound probe. Previously described age-appropriate depths were referenced and used to insonate the middle cerebral artery.¹¹ One registered vascular technologist, with more than 10 yr of experience with transcranial Doppler, insonated the middle cerebral arteries during cerebral autoregulation testing (performed by Y.U.). At the time of testing, both of these parties were blinded to TBI severity. Cerebral autoregulation was calculated off-line and entered into our database by S.S.F. or M.S.V.

Testing and Quantifying Cerebral Autoregulation (Main Outcome)

Study participants underwent static autoregulation testing after TBI as previously described.¹² Briefly, during steady state (technically satisfactory conditions where change or lack of change in V_{mca} is attributed to increase in CPP; usually within 10 s), intravenous phenylephrine was titrated using a slow infusion ($0.05\text{--}0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) over a 3- to 5-min period. CPP was increased according to whichever following variable was greater: (1) 20% above baseline; or (2) a set value of 80 mmHg for the group younger than 9 yr and 90 mmHg for the group aged 9–16 yr, respectively. CPP and V_{mca} were simultaneously and continuously measured and were recorded in the computer for subsequent off-line analysis.

Autoregulatory capacity was quantified with the ARI, which was calculated according to a previously published formula.¹² Mathematically, the ARI is the percent change in estimated cerebrovascular resistance per percent change in CPP:

ARI

$$= \% \Delta \text{Estimated Cerebrovascular Resistance} / \% \Delta \text{CPP.}$$

The estimated cerebrovascular resistance is the ratio of CPP to V_{mca} . Therefore, an ARI of 0 represents absent autoregulation (pressure-dependent V_{mca}), 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 or greater.¹²

Patient Outcome (Secondary Outcome)

Glasgow outcome score was determined at 12 months after TBI using either telephone or written questionnaires or in-person evaluations by a research nurse blinded to clinical data determined outcome. The Jennett five-point GOS classification was used¹³: GOS 1 = dead; GOS 2 = vegetative state, GOS 3 = alive but functionally impaired, GOS 4 = minimal handicap, and GOS 5 = premorbid level of functioning. A GOS less than 4 reflected poor outcome, whereas good outcome was defined as a GOS of 4 or 5.¹³

Statistical Analysis

Patients who underwent cerebral autoregulation testing during the first 72 h after TBI were considered for this analysis. SPSS version 11.5 (SPSS Inc., Chicago, IL) was used for data entry and analysis. Descriptive statistics were used to describe patient characteristics, clinical data, differences in cerebral autoregulation, intracranial pressure (ICP), and factors associated with long-term outcome.

Impaired cerebral autoregulation (main outcome) was defined using both (1) average ARI of both cerebral hemispheres (mean ARI [*mARI*]) and (2) lowest ARI (*lARI*) of either cerebral hemisphere. Patients were categorized as having either impaired (ARI <0.4) or intact (ARI \geq 0.4) autoregulation by each definition. Based on our previous work showing hemispheric differences in cerebral autoregulation, and because final outcome may be determined by severity of TBI and worst autoregulation, an *lARI* less than 0.4 defined impaired cerebral autoregulation.

The Student *t* test, chi-square test, or Fisher exact test was used to analyze differences in baseline characteristics, physiologic conditions, and autoregulation data between (1) young (aged <4 yr) and older (aged \geq 4 yr) children, (2) impaired (*lARI* <0.4) *versus* intact (*lARI* \geq 0.4) cerebral autoregulation, and (3)

good (GOS ≥ 4) versus poor (GOS < 4) outcome. The relation between impaired cerebral autoregulation and (1) sedation type, (2) ICP greater than 20 mmHg, and (3) V_{mca} greater than 2 SDs was determined by the Fisher exact test. Patients were also divided into two groups, (1) poor outcome (12-month GOS < 4) and (2) good outcome (12-month GOS ≥ 4), to examine the relation between age, cerebral autoregulation, and outcome. These data are presented as mean \pm SD or n (%). $P < 0.05$ reflects significance. Linear relations between IARI and age as well as IARI and GCS at time of autoregulation testing were examined using the Spearman rank correlation and are reported using R^2 and P values.

To determine potential factors independently associated with impaired cerebral autoregulation, variables with significance or variables with trends toward significance ($0.05 \leq P < 0.10$) for impaired IARI were entered into a binary logistic regression model for multivariate analysis. Adjusted odds ratios and 95% confidence intervals for the relation between variables of interest and impaired cerebral autoregulation (IARI) were determined.

Results

Study Participants

During the 5-yr study period, 140 children were eligible for enrollment in the larger ongoing National Institutes of Health-funded study examining cerebral autoregulation and quality of life in children with TBI. We did not capture 42 (38 patients were extubated before consent) study participants, leaving 98 families available for approach. Sixteen guardians did not consent. Forty-five patients were then excluded from this analysis based on the following criteria: brain death ($n = 1$) or death ($n = 6$) before autoregulation testing, autoregulation testing greater than 72 h after injury date ($n = 20$), language barriers ($n = 5$), hemodynamic instability (as determined by the treating intensivist; $n = 6$), no available guardian ($n = 6$), and mild TBI ($n = 1$). Consequently, data from 37 children who underwent cerebral autoregulation testing within the first 72 h after moderate to severe TBI were examined. All 37 patients completed the protocol without dropout or withdrawal. Data from 12 children have previously been published in a study designed to answer a different question.⁴

Demographic and Baseline Clinical Characteristics

Children were 8.9 ± 5.1 (0.8–16) yr old (table 1). Ten children (27%) were young (aged < 4 yr; mean, 2.0 yr; median, 2.2 yr; range, 0–3 yr), and 27 children (73%) were older (aged ≥ 4 yr; mean, 11.4 yr; median, 12.0 yr; range, 4–16 yr). The number of boys exceeded the number of girls in both age groups. Two children had

Table 1. Clinical Data of 37 Children with Moderate to Severe Traumatic Brain Injury

	Age, yr	8.9 ± 5.1 (0.8–16.0)
Male		26 (70)
Mechanism of injury		
Motor vehicle crash		8 (22)
Fall		9 (24)
Auto-pedestrian		5 (13.5)
Inflicted trauma		2 (5)
Bike		5 (13.5)
Other		8 (22)
Associated injuries*		
None		17 (46)
Orthopedic		20 (54)
Abdominal/pulmonary		8 (22)
Traumatic brain injury on computed tomography in emergency department*		
Diffuse axonal injury		4 (11)
Subdural hematoma		16 (43)
Epidural hematoma		7 (19)
Subarachnoid hemorrhage		15 (41)
Intracerebral hemorrhage		6 (16)
Cerebral edema		3 (8)
Skull fracture		22 (60)
Cerebral infarction		2 (5)
In-hospital mortality		2 (5.4)
12-month Glasgow outcome score		3.9 ± 1.1 (1–5)

Data are presented as mean \pm SD (range) or n (%).

* Percentages exceed 100% because some patients have multiple injuries.

inflicted trauma. All patients received a head computed tomography scan in the emergency department. All children had moderate to severe TBI (GCS 3–12) at the time of admission to the emergency department. Intracranial pressure data were available in 30 patients (81%) at the time of cerebral autoregulation testing. There were no demographic or morphometric differences between patients with and without ICP monitoring or between the patients included ($n = 37$) and excluded ($n = 45$) in this study (table 1).

Cerebral Autoregulation Data

All patients underwent cerebral autoregulation testing within 72 h (15 ± 17 h; range, 0–72 h) after pediatric intensive care unit admission. Three patients (30%) in the young group and 6 patients (22%) in the older group underwent neurosurgery during the first 72 h after TBI (Fisher $P = 0.6$), but none of the children had autoregulation testing within 6 h of receiving general anesthesia. The distribution of mannitol (M) and/or 3% hypertonic saline (HS) either before or at the time of autoregulation testing was 9/10 (7M and 2M/HS; $P = 0.6$) in the young group versus 24/27 (15M and 9M/HS; $P = 1.0$) in the older group. There were no adverse outcomes due to autoregulation testing.

Overall, children had intact cerebral autoregulation (table 2). However, children younger than 4 yr had lower autoregulatory indices than older children (table 2). Children younger than 4 yr had a higher incidence of

Table 2. Differences in Cerebral Autoregulation between Younger and Older Children (n = 37) with Moderate to Severe Traumatic Brain Injury

	All Children (n = 37)	Younger: Aged <4 yr (n = 10)	Older: Aged ≥4 yr (n = 27)	P Value
Baseline characteristics				
Age, yr	8.9 ± 5.1	2.2 ± 0.8	11.4 ± 3.4	<0.01*
Range	0–16	0–3	4–16	
Male	26 (70)	6 (60)	20 (74)	0.44
Admission Glasgow Coma Scale score	4.7 ± 1.8	4.1 ± 1.2	4.9 ± 2.0	0.23
12-month Glasgow outcome score	3.8 ± 1.1	3.0 ± 1.3	4.1 ± 0.9	0.02*
Conditions at time of autoregulation testing				
Postinjury date, days	0.62 ± 0.7	0.60 ± 0.70	0.63 ± 0.74	0.91
Glasgow Coma Scale score	6.1 ± 1.7	5.8 ± 1.6	6.2 ± 1.8	0.50
Paco ₂ , mmHg	35.5 ± 3.7	34.3 ± 3.7	35.9 ± 3.7	0.24
Hematocrit, %	30.1 ± 4.9	31.7 ± 5.8	29.4 ± 4.5	0.22
Temperature, °C	37.7 ± 0.7	37.7 ± 0.8	37.8 ± 0.7	0.74
Mean arterial pressure, mmHg	74.3 ± 14.0	72.7 ± 10.4	74.9 ± 15.3	0.68
ICP, mmHg	17.4 ± 11.5	22.1 ± 19.9	14.2 ± 9.2	0.25
Number of patients with ICP >20 mmHg	10 (27)	4 (40)	6 (22)	0.41
Number of patients with hyperemia, V _{mca} >2 SDs	7 (19)	2 (20)	5 (19)	1.00
Autoregulation data				
mARI	0.6 ± 0.3	0.48 ± 0.33	0.69 ± 0.32	0.09
lARI	0.5 ± 0.4	0.28 ± 0.40	0.57 ± 0.37	0.05
Number of patients with impaired autoregulation				
mARI†	10 (27), 0.27 (0.12–0.42)	4 (40), 0.40 (0.06–0.74)	6 (22), 0.22 (0.06–0.38)	0.41
lARI†	15 (41), 0.41 (0.25–0.57)	8 (80), 0.80 (0.51–1.09)	7 (26), 0.26 (0.09–0.43)	0.006*

Data are presented as mean ± SD or n (column %). Postinjury date 0 = day of injury.

* Significant difference between age <4 yr and age ≥4 yr groups. † Data are presented as n (column %) and mean population estimate (95% confidence interval).

ICP = intracranial pressure; lARI = lowest autoregulatory index; mARI = mean autoregulatory index; Paco₂ = arterial carbon dioxide tension; V_{mca} = middle cerebral artery flow velocity (cm/s).¹¹

impaired cerebral autoregulation than older children (8 of 10 vs. 7 of 27; $P = 0.006$). There was no linear relation between age and lARI. However, higher GCS at the time of autoregulation testing was associated with higher lARI (fig. 1, actual data shown; $r^2 = 0.49$ based on rank, $P = 0.002$).

There was no difference in admission GCS, arterial carbon dioxide tension (Paco₂), hematocrit, temperature, ICP, hyperemia, or mean arterial pressure between young and older children during the time of cerebral autoregulation testing (table 2). There was no difference in increase in CPP between young and older children ($R^2 = 0.2$). Sedation regimens were determined by the treating clinicians, and typical practice is to use benzo-

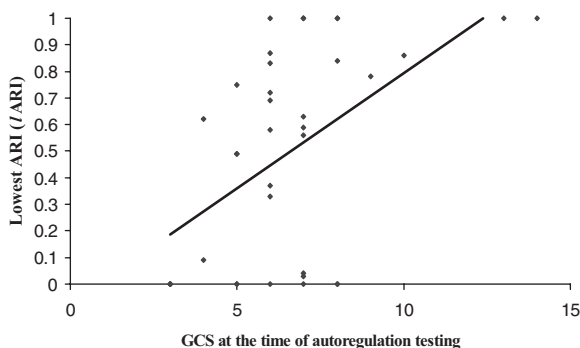


Fig. 1. Relation between Glasgow Coma Scale (GCS) score and cerebral autoregulation (lowest autoregulatory index [lARI]).

diazepine sedation followed by propofol for brief periods for refractory agitation and/or ICP. At the time of cerebral autoregulation testing, 29 children received sedation with a combination of either (1) an intravenous benzodiazepine (midazolam or lorazepam) and fentanyl (n = 19, 66%) or (2) an intravenous propofol (n = 10, 34%). There was no association between type of sedation and impaired cerebral autoregulation. Six (16%) of 37 patients had fever (temperature ≥38.5°C) during the time of autoregulation testing, and 4 patients (67%) with fever had impaired cerebral autoregulation (lARI 0.32 ± 0.38; range, 0–0.89). Absolute hyperemia, defined as V_{mca} greater than 2 SDs for age and sex,^{11,14,15} was present in 7 of 37 patients (19%), and there was no association between hyperemia and impaired (n = 2/15; 13%) cerebral autoregulation ($P = 0.68$; table 3). In each case where ICP monitoring was discontinued before cerebral autoregulation testing (7 of 37 patients), the ICP was less than 10 mmHg, so the mean arterial pressure was used as the CPP.

Factors Associated with Impaired Cerebral Autoregulation

Univariate factors associated with impaired cerebral autoregulation (lARI <0.4) included age less than 4 yr ($P = 0.01$) and lower GCS score at time of autoregulation testing ($P = 0.03$; table 3). Factors independently associated with impaired cerebral autoregulation were age

Table 3. Differences in Patient Characteristics between Impaired and Intact Cerebral Autoregulation Using IARI

	Impaired (n = 15)	Intact (n = 22)	P Value
Baseline characteristics			
Age, yr	6.1 ± 5.3	10.8 ± 4.1	0.01
Age <4 yr	8 (53)	2 (9)	0.01
Male*	8 (53)	18 (82)	0.08
Admission Glasgow Coma Scale score	4.2 ± 1.4	5.1 ± 2.0	0.17
12-month Glasgow outcome score	3.3 ± 1.5	4.2 ± 0.6	0.07
Conditions at time of autoregulation testing			
Postinjury date, days	0.73 ± 0.80	0.55 ± 0.67	0.44
Glasgow Coma Scale score	5.4 ± 1.8	6.7 ± 1.5	0.03
Number of patients with propofol sedation*	2 (13)	8 (36)	0.15
Paco ₂ , mmHg	35.5 ± 3.7	35.5 ± 3.8	0.98
Hyperventilation, Paco ₂ <35 mmHg*	8 (53)	12 (55)	0.94
Hematocrit, %	30.9 ± 5.5	29.5 ± 4.4	0.37
Temperature, °C	37.9 ± 0.8	37.7 ± 0.6	0.41
Fever, temperature ≥38.5°C	4 (27)	2 (9)	0.20
Number of patients with hyperemia, V _{mca} >2 SDs	2 (13)	5 (23)	0.68
Mean arterial pressure, mmHg	74 ± 12	74 ± 15	0.98
ICP, mmHg	21 ± 17	14 ± 10	0.11
Number of patients with ICP >20 mmHg*	5 (33)	5 (23)	0.71
Autoregulation data			
mARI	0.28 ± 0.21	0.87 ± 0.12	<0.01
IARI	0.06 ± 0.12	0.79 ± 0.18	<0.01

* Data are presented as column %.

ICP = intracranial pressure; IARI = lowest autoregulatory index; mARI = mean autoregulatory index; Paco₂ = arterial carbon dioxide tension; V_{mca} = middle cerebral artery flow velocity (cm/s).¹¹

less than 4 yr (adjusted odds ratio, 12.2; 95% confidence interval, 1.5–98.5) and lower GCS at the time of autoregulation testing (adjusted odds ratio for higher GCS, 0.53; 95% confidence interval, 0.30–0.96; table 4). Age less than 4 yr predicted impaired cerebral autoregulation with a sensitivity of 53% and a specificity of 91%. GCS less than 9 predicted impaired cerebral autoregulation with a sensitivity of 100% and a specificity of 18%. Intracranial hypertension (ICP >20 mmHg) or hyperemia was not associated with impaired cerebral autoregulation.

Twelve-month Glasgow Outcome Score

Glasgow outcome scores were available in 30 patients (84%). The overall 12-month GOS score for these patients was 3.9 ± 1.1 (range, 1–5; table 1). Eight children (27%) had a poor outcome (table 5). Children younger than 4 yr had a worse outcome than older children (GOS 3.0 ± 1.3 vs. 4.1 ± 0.9; P = 0.02). Poor outcome was

Table 4. Multivariate Analysis of Factors Independently Associated with Impaired Cerebral Autoregulation (by Lowest Autoregulatory Index) after Moderate to Severe Pediatric Traumatic Brain Injury

	AOR (95% CI)	P Value
Age <4 yr	12.2 (1.52–98.5)	0.02
Glasgow Coma Scale score at time of autoregulation testing	0.53 (0.30–0.96)	0.04
Male sex	0.14 (0.02–1.1)	0.05

AOR = adjusted odds ratio; CI = confidence interval.

associated with lower autoregulatory indices and impaired cerebral autoregulation (table 5). There was no difference in demographic characteristics between the 30 patients with cerebral autoregulation and GOS data and the 7 patients for whom we did not have outcome data.

Discussion

The main findings of this study are that age less than 4 yr and low GCS score at the time of autoregulation testing were independently associated with impaired cerebral autoregulation. We also found that children younger than 4 yr and children with impaired cerebral autoregulation had worse 12-month GOS. These findings are the first to describe age as an independent risk factor for impaired cerebral autoregulation in children early after TBI.

Despite the relatively small number of patients in this study, the current analysis shows that children younger than 4 yr had lower autoregulatory indices, a higher prevalence of impaired cerebral autoregulation, and worse long-term outcome (table 2). We defined young children as children younger than 4 yr to examine the relation between age and impaired cerebral autoregulation because children aged 0–4 yr have the highest rate for TBI-related deaths, hospitalizations, and emergency department visits compared with any other age group in the United States.⁷ Furthermore, we did not observe a linear relation between age and impaired cerebral auto-

Table 5. Factors Associated with 12-Month Glasgow Outcome Score in 30 Patients*

	GOS <4 (n = 8)	GOS >4 (n = 22)	P Value
Baseline characteristics			
Age, yr	6.1 ± 6.1 (0.8–15.0)	10.4 ± 4.0 (3.0–16.0)	0.10
Male†	6 (75)	15 (68)	1.00
Autoregulation data			
Admission Glasgow Coma Scale score	3.9 ± 1.0 (3.0–5.0)	5.5 ± 2.0 (3.0–9.0)	0.04
mARI	0.38 ± 0.36 (0–1.0)	0.72 ± 0.30 (0–1.0)	0.01
lARI	0.20 ± 0.37 (0–1.0)	0.60 ± 0.36 (0–1.0)	0.01
Number of patients with impaired autoregulation			
mARI†	5 (63)	3 (14)	0.02
lARI†	6 (75)	5 (23)	0.03
Number of patients with absent autoregulation			
Both cerebral hemispheres†	2 (25)	1 (5)	0.17
One cerebral hemisphere†	4 (50)	3 (14)	0.06

Data are presented as mean ± SD (range) or n (%). Glasgow outcome score (GOS) <4 = poor outcome.

* Seven patients with missing GOS data. † Data are presented as column %.

lARI = lowest autoregulatory index; mARI = mean autoregulatory index.

regulation. We speculate that the higher incidence of impaired cerebral autoregulation in young children at least partially explains the relation between young age and poor outcome, thereby making young age an important confounder in the causal pathway between cerebral autoregulation and outcome (fig. 2). Although this study does not provide a mechanistic explanation for the relation between either young age and impaired cerebral autoregulation, or impaired cerebral autoregulation and poor outcome, these observations provide new neuro-epidemiologic data of some cerebrovascular changes after pediatric TBI and may provide the rationale for further examining age-related differences in cerebral autoregulatory mechanisms and response after pediatric TBI.

Fluid percussion injury in animals is thought to mimic

pediatric TBI,¹⁶ and studies of fluid percussion injury in piglets indicate age-related differences in both the incidence of impaired autoregulation and mechanisms regulating autoregulatory capacity. When compared with older juvenile piglets with fluid percussion injury, newborn piglets with fluid percussion injury have a higher incidence of impaired autoregulation and possible unique biologic autoregulatory mechanisms.^{17,18} Cell signaling pathways, endogenous peptides, and membrane potentials have been examined as mechanisms of vascular control of cerebral autoregulatory capacity.¹⁷⁻¹⁹ Increased endothelin-1 levels¹⁸; blunted K⁺ channel activation¹⁷; and decreased levels of nitric oxide, cyclic guanosine monophosphate, cyclic adenosine monophosphate, and prostanoids^{19,20} have been reported in new-

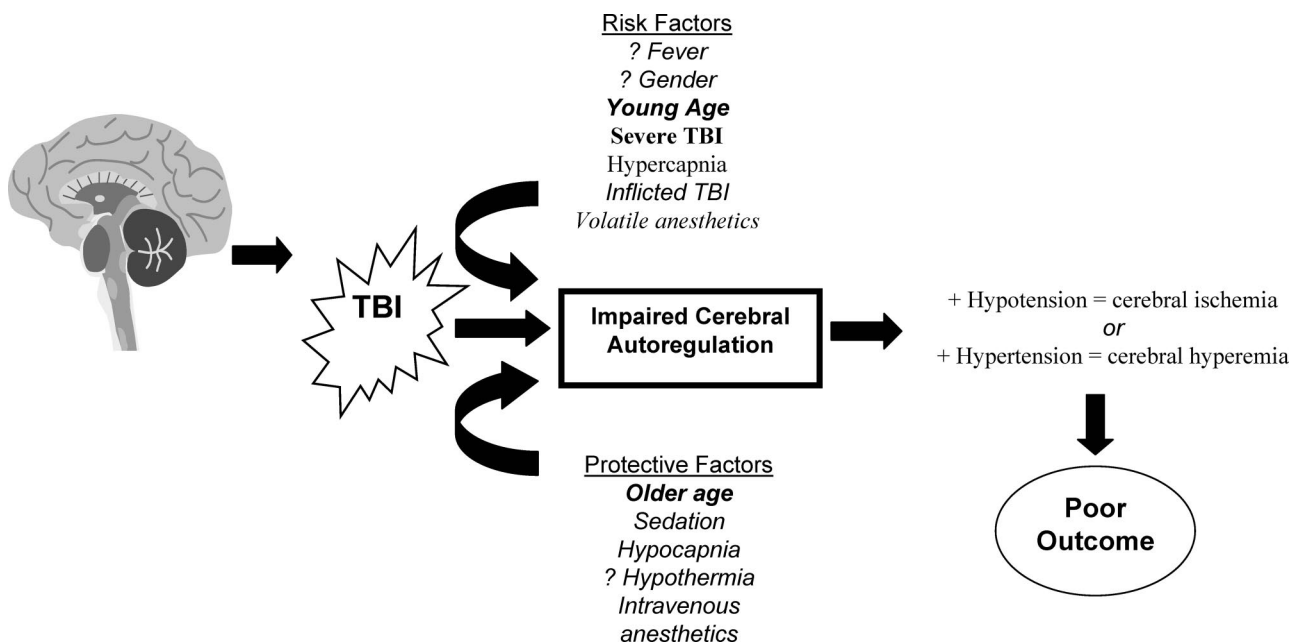


Fig. 2. Suggested causal pathway for the role of impaired cerebral autoregulation in determining outcome after pediatric traumatic brain injury (TBI) and of the potential major clinical confounders of cerebral autoregulation. ? = possible factor. Actual data are shown, but correlation is based on rank.

born *versus* juvenile piglets after fluid percussion injury when subjected to hemorrhagic hypotension as the autoregulatory stimulus. Potential mechanisms that might contribute to age-related differences in autoregulatory outcome status include age-related up-regulation of endothelin 1, which impairs K^+ channel function, an important mechanism for vasodilation.^{17,18} Age differences in autoregulatory mechanisms likely exist similarly in humans and thus merit further study.

Cerebral autoregulatory status may be an important marker of or, more importantly, a contributor to injury severity in children with TBI. Although previous studies by Sharples *et al.*⁹ and Vavilala *et al.*⁶ described a high incidence of impaired cerebral autoregulation in children with moderate and severe TBI, admission GCS was used to describe the cohort, and the incidence of impairment was not examined in relation to GCS at the time of testing. Although age was also an independent predictor of impaired cerebral autoregulation at the time of testing, unlike age, GCS and cerebral autoregulation may improve or deteriorate early after TBI.²¹ This fact and the fact that patients with severe TBI have more impairment than patients with mild TBI⁶ suggest that point-of-care evaluation of GCS may serve as a screening tool for impaired cerebral autoregulation when formal autoregulation testing is not feasible. However, a larger study is needed to verify these preliminary findings.

A small case series suggests that children with inflicted TBI may be at greater risk for impaired cerebral autoregulation and poor outcome than children with TBI from other causes, but the mechanisms explaining this association are not well defined and the number of children with inflicted TBI was exceedingly small.²² Cerebrospinal fluid and serum markers of neuronal damage such as S100B and neuronal specific enolase are found differentially and in higher concentrations in inflicted TBI compared with noninflicted TBI, suggesting either a more severe form or a different type of TBI²³ and potentially a different mechanism involved in impaired cerebral autoregulation after inflicted TBI.

Certain physiologic factors may also affect cerebral autoregulatory capacity after TBI (fig. 2). $Paco_2$ is the most potent cerebral vasodilator, increasing CBF linearly by 2–4% per mmHg $Paco_2$ within a 25- to 75-mmHg range.²⁴ However, carbon dioxide reactivity can be temporarily impaired after TBI,²⁵ and carbon dioxide reactivity changes of less than 2% may be associated with poor outcome after TBI.²⁶ In our study, there was no association between $Paco_2$ and cerebral autoregulation, but the number of children with either hypocapnia or hypercapnia was very small (table 3). Hyperthermia may also be an independent predictor of injury severity²⁷ and may be associated with poor outcome after pediatric TBI.²⁸ Although we found no difference in temperature between children with and without impaired cerebral

autoregulation, few children had fever at the time of testing (table 3).

Severe pediatric TBI can lead to increased CBF²⁹ and hyperemia in the presence of impaired cerebral autoregulation.^{6,8} In 1996, Biagas *et al.*³⁰ showed that posttraumatic hyperemia may be an age-related trend in immature (3.5- to 4.5-week-old) rats and suggested variations in vasoreactivity or metabolism as a possible mechanism. In our study, young children did not have a higher incidence of cerebral hyperemia than children aged 4 yr and older (table 2). Although we compared our V_{mca} data to age- and sex-specific reference values,^{11,14} our definition of cerebral hyperemia was not ideal because we did not have a measure of cerebral metabolic rate. While adult and pediatric studies document an association between hyperemia and loss of cerebral autoregulation,^{6,31} we found no such association. Low cerebrovascular resistance results in vasodilatation and higher CBF, and limits cerebral vasoconstriction during hypertension. Overall, the number of patients with cerebral hyperemia in our cohort was small, and a true association between hyperemia and loss of autoregulation cannot be determined from this data set.

The primary limitation of this study is the small sample size, reducing our ability to better examine the relation between age and cerebral autoregulation. Transcranial Doppler ultrasonography measures V_{mca} , not CBF. However, changes in CBF velocity are proportional to changes in CBF,³² and transcranial Doppler is a noninvasive bedside method for estimation of CBF in children. Furthermore, transcranial Doppler is commonly used to measure cerebral blood flow velocity and autoregulatory capacity.^{6,33} Many of our patients received sedation, which may (in particular propofol) decrease CBF and improve autoregulation.³⁴ However, we found no relation between autoregulation and type of sedation. In the current study, there were only two patients with inflicted TBI, and we cannot comment on the relative contribution of age *versus* inflicted TBI on impaired cerebral autoregulation. Given the small sample size and the observational (and not randomized) nature of this study, we have not altered our treatment strategy. Finally, mechanistic explanations of the observed age-related differences are lacking. Despite these limitations, these data suggest a need to further examine the age-related mechanisms involved in cerebral autoregulation in children with TBI. Perhaps the most important consequence of this study is that we now have an increased awareness that young children may have an increased risk of impaired cerebral autoregulation; thereby prompting autoregulation testing in these younger children, early after TBI.

In summary, our data show that children younger than 4 yr have an increased risk of impaired cerebral autoregulation, independent of GCS at the time of autoregulation testing. Developmental age-related factors may play

a role in the mechanisms maintaining or worsening this homeostatic process in children with TBI. Understanding alterations in these mechanisms may be important to improving the cerebrovascular milieu and, ultimately, the outcome of young children, who are at most risk of poor outcome after TBI.

The authors thank the children and families at Harborview Medical Center who participated in this study and Domonique Calhoun, M.F.A. (Secretary Senior, Department of Anesthesiology, Harborview Medical Center, Seattle, Washington), for her assistance in the preparation of the manuscript.

References

- Paulson OB, Strandgaard S, Edvinsson L: Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990; 2:161-92
- Sahuquillo J, Munar F, Bagueña M, Poca MA, Pedraza S, Rodriguez-Baeza A.: Evaluation of cerebrovascular CO₂-reactivity and autoregulation in patients with post-traumatic diffuse brain swelling (diffuse injury III). *Acta Neurochir Suppl* 1998; 71:233-6
- Junger EC, Newell DW, Grant GA, Avellino AM, Ghatan S, Douville CM, Lam AM, Aaslid R, Winn HR: Cerebral autoregulation following minor head injury. *J Neurosurg* 1997; 86:425-32
- Vavilala MS, Muangman S, Tontisirin N, Fisk D, Roscigno C, Mitchell P, Kirkness C, Zimmerman JJ, Chesnut R, Lam AM: Impaired cerebral autoregulation and 6-month outcome in children with severe traumatic brain injury: Preliminary findings. *Dev Neurosci* 2006; 28:348-53
- Obrist WD, Gennarelli TA, Segawa H, Dolinskas CA, Langfitt TW: Relation of cerebral blood flow to neurological status and outcome in head-injured patients. *J Neurosurg* 1979; 51:292-300
- Vavilala MS, Lee LA, Boddu K, Visco E, Newell DW, Zimmerman JJ, Lam AM: Cerebral autoregulation in pediatric traumatic brain injury. *Pediatr Crit Care Med* 2004; 5:257-63
- Rutland-Brown W, Langlois JA, Thomas KE, Xi YL: Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil* 2006; 21:544-8
- 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; 71:72-6
- Sharples PM, Matthews DS, Eyre JA: Cerebral blood flow and metabolism in children with severe head injuries: II. Cerebrovascular resistance and its determinants. *J Neurol Neurosurg Psychiatry* 1995; 58:153-9
- Armstead WM, Kurth CD: Different cerebral hemodynamic responses following fluid percussion brain injury in the newborn and juvenile pig. *J Neurotrauma* 1994; 11:487-97
- Bode H: Applications of Pediatric Transcranial Doppler Ultrasonography. New York, Springer Verlag Wein, 1988, p. 114
- Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW: Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. *ANESTHESIOLOGY* 1995; 83:66-76
- Jennett B, Teasdale G, Galbraith S, Braakman R, Avezaat C, Minderhoud J, Heiden J, Kurze T, Murray G, Parker L: Prognosis in patients with severe head injury. *Acta Neurochir Suppl (Wien)* 1979; 28:149-52
- Vavilala MS, Kincaid MS, Muangman SL, Suz P, Rozet I, Lam AM: Gender differences in cerebral blood flow velocity and autoregulation between the anterior and posterior circulations in healthy children. *Pediatr Res* 2005; 58:574-8
- Tontisirin N, Muangman SL, Suz P, Pihoker C, Fisk D, Moore A, Lam AM, Vavilala MS: Early childhood gender differences in anterior and posterior cerebral blood flow velocity and autoregulation. *Pediatrics* 2007; 119:e610-5
- Gennarelli TA: Animate models of human head injury. *J Neurotrauma* 1994; 11:357-68
- Armstead WM: Age-dependent impairment of K(ATP) channel function following brain injury. *J Neurotrauma* 1999; 16:391-402
- Armstead WM: Role of endothelin-1 in age-dependent cerebrovascular hypotensive responses after brain injury. *Am J Physiol* 1999; 277:H1884-94
- Armstead WM: Role of impaired cAMP and calcium-sensitive K⁺ channel function in altered cerebral hemodynamics following brain injury. *Brain Res* 1997; 768:177-84
- Armstead WM: Cerebral hemodynamics after traumatic brain injury of immature brain. *Exp Toxicol Pathol* 1999; 51:137-42
- Tontisirin N, Armstead W, Waitayawinyu P, Moore A, Udomphorn Y, Zimmerman JJ, Chesnut R, Vavilala MS: Change in cerebral autoregulation as a function of time in children after severe traumatic brain injury: A case series. *Childs Nerv Syst* 2007; 23:1163-9
- Vavilala MS, Muangman S, Waitayawinyu P, Roscigno C, Jaffe K, Mitchell P, Kirkness C, Zimmerman JJ, Ellenbogen R, Lam AM: Neurointensive care; impaired cerebral autoregulation in infants and young children early after inflicted traumatic brain injury: A preliminary report. *J Neurotrauma* 2007; 24:87-96
- Berger RP, Dulani T, Adelson PD, Leventhal JM, Richichi R, Kochanek PM: Identification of inflicted traumatic brain injury in well-appearing infants using serum and cerebrospinal markers: A possible screening tool. *Pediatrics* 2006; 117:325-32
- Severinghaus JW, Lassen N: Step hypocapnia to separate arterial from tissue PCO₂ in the regulation of cerebral blood flow. *Circ Res* 1967; 20:272-8
- Cold GE, Jensen FT, Malmros R: The cerebrovascular CO₂ reactivity during the acute phase of brain injury. *Acta Anaesthesiol Scand* 1977; 21:222-31
- Adelson PD, Clyde B, Kochanek PM, Wisniewski SR, Marion DW, Yonas H: Cerebrovascular response in infants and young children following severe traumatic brain injury: A preliminary report. *Pediatr Neurosurg* 1997; 26:200-7
- Natale JE, Joseph JG, Helfaer MA, Shaffner DH: Early hyperthermia after traumatic brain injury in children: Risk factors, influence on length of stay, and effect on short-term neurologic status. *Crit Care Med* 2000; 28:2608-15
- Suz P, Vavilala MS, Souter M, Muangman S, Lam AM: Clinical features of fever associated with poor outcome in severe pediatric traumatic brain injury. *J Neurosurg Anesthesiol* 2006; 18:5-10
- Sharples PM, Stuart AG, Matthews DS, Aynsley-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* 1995; 58:145-52
- Biagas KV, Grundl PD, Kochanek PM, Schiding JK, Nemoto EM: Posttraumatic hyperemia in immature, mature, and aged rats: Autoradiographic determination of cerebral blood flow. *J Neurotrauma* 1996; 13:189-200
- McCulloch TJ, Visco E, Lam AM: Graded hypercapnia and cerebral autoregulation during sevoflurane or propofol anesthesia. *ANESTHESIOLOGY* 2000; 93:1205-9
- Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM: Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994; 25:1985-8
- Mandera M, Larysz D, Wojtacha M: Changes in cerebral hemodynamics assessed by transcranial Doppler ultrasonography in children after head injury. *Childs Nerv Syst* 2002; 18:124-8
- Karsli C, Luginbuehl I, Farrar M, Bissonnette B: Propofol decreases cerebral blood flow velocity in anesthetized children. *Can J Anaesth* 2002; 49:830-4