Age-related carbon dioxide reactivity in children after moderate and severe traumatic brain injury

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OBJECTIVE The objective of this study is to assess carbon dioxide reactivity (CO₂R) in children following traumatic brain injury (TBI).

METHODS This prospective observational study enrolled children younger than 18 years old following moderate and severe TBI. Thirty-eight mechanically ventilated children had daily CO₂R testing performed by measuring changes in their bilateral middle cerebral artery flow velocities using transcranial Doppler ultrasonography (TCD) after a transient increase in minute ventilation. The cohort was divided into 3 age groups: younger than 2 years (n = 12); 2 to 5 years old (n = 9); and older than 5 years (n = 17).

RESULTS Children younger than 2 years old had a lower mean CO₂R over time. The 2–5-year-old age group had higher mean CO₂R than younger patients (p = 0.01), and the highest CO₂R values compared with either of the other age groups (vs > 5 years old, p = 0.046; vs < 2 years old, p = 0.002). Having a lower minimum CO₂R had a statistically significant negative effect on outcome at discharge (p = 0.0413). Impaired CO₂R beyond Postinjury Day 4 trended toward having an effect on outcome at discharge (p = 0.0855).

CONCLUSIONS Abnormal CO₂R is prevalent in children following TBI, and the degree of impairment varies by age. No clinical or laboratory parameters were identified as risk factors for impaired CO₂R. Lower minimum CO₂R values are associated with worse outcome at discharge.

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KEY WORDS pediatric traumatic brain injury; carbon dioxide reactivity; transcranial Doppler ultrasound; cerebrovascular reactivity; trauma

TRAUMATIC brain injury (TBI) is the leading cause of disability and death in children in the United States and accounts for more than 2600 deaths and 37,000 hospitalizations per year.⁶ Severe TBI management guidelines recommend targeting age-specific cerebral perfusion pressure (CPP), managing intracranial hypertension (ICH), and minimizing secondary brain injury through the avoidance of hypoxia, hypotension, hyperthermia, hyperglycemia, and hypo- or hypercarbia.^{12,27} Despite these management strategies, there has been little improvement in neurological outcomes after severe TBI over the past 2 decades.²⁵ Among the pediatric age group, there is a

difference in outcome with increasing age.^{3,7,15,16} In particular, children younger than 2 years may have worse outcomes than older children.^{1,2} A greater understanding of the pathophysiological changes that occur in the pediatric brain following moderate and severe TBI is needed to identify alternative, additional, or individualized treatment approaches that may benefit these children.

Cerebrovascular reactivity (CVR) reflects the normal response of the cerebral arterioles to changes in physiological stimuli, such as the partial pressure of arterial carbon dioxide (PaCO₂). Under normal conditions, increased concentrations of PaCO₂ result in the vasodilation

ABBREVIATIONS AHT = abusive head trauma; CBF = cerebral blood flow; CO₂R = carbon dioxide reactivity; CPP = cerebral perfusion pressure; CVR = cerebrovascular reactivity; ETCO₂ = end-tidal CO₂; GCS = Glasgow Coma Scale; GOS-E Peds = Glasgow Outcome Scale Extended Pediatric Version; ICH = intracranial hypertension; ICP = intracranial pressure; MOI = mechanism of injury; PaCO₂ = partial pressure of arterial carbon dioxide; PID = Postinjury Day; ROC = receiver operator characteristic; TBI = traumatic brain injury; TCD = transcranial Doppler ultrasonography; V_{MCA} = mean blood flow velocity of the right and left middle cerebral arteries.

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of these vessels with the subsequent increase in cerebral blood flow (CBF),^{9,32} while decreased concentrations of PaCO₂ have the opposite effect. Additionally, CO₂ reactivity (CO₂R) and CBF are higher at baseline in children than adults.^{10,14,26,29,31,33} These expected vasomotor responses to changes in PaCO₂ can be affected by several pathological processes, including TBI. Impaired CVR may result in cerebral hyperemia or ischemia with changes in CPP. Children may have less tolerance for alterations in cerebral hemodynamics and thus be at higher risk for sustaining secondary brain injury. Multiple studies in adults have shown a link between impaired CO₂R and poor neurological outcomes.^{8,13,21,28} Much less is known about CO₂R impairment and its effects on outcome following TBI in children.

It is important to understand how vasoreactivity is altered in children after TBI and the relationship between decreased CO₂R and outcomes. Thus, we sought to 1) describe differences in the temporal pattern and prevalence of impaired CO₂R in different age groups after moderate and severe TBI; 2) examine if predictors of outcome after head injury such as age, Glasgow Coma Scale (GCS) score, and intracranial pressure (ICP) are important determinants of impaired CO₂R; and 3) correlate impaired CVR with outcome as measured by the Glasgow Outcome Scale Extended Pediatric Version (GOS-E Peds) at discharge and the 3-month follow-up.

Methods

Study Population

This study was part of a larger prospective observational study of children with TBI that was performed at a tertiary care, Level 1, pediatric trauma center. The study was approved by the institutional review board of The Research Institute at Nationwide Children's Hospital, and informed consent was obtained from parents before enrollment. Children between the ages of 1 day and 17 years who were admitted to the pediatric intensive care unit with a diagnosis of moderate to severe head trauma (postresuscitation GCS score ≤ 12), abnormal head imaging, and tracheal intubation were included. Children were excluded if they were deemed to have suffered a nonsurvivable injury, had a GCS score of 3 with fixed and dilated pupils, and death was imminent. Children were also excluded if they had a previous diagnosis of severe developmental disability or mental retardation because the interpretation of clinical outcome would be difficult. Demographic data including age, sex, mechanism of injury (MOI), Injury Severity Score, and postresuscitation GCS score were obtained.

Clinical Management Protocol

Patients with severe TBI were treated according to the 2012 guidelines for the acute medical management of severe pediatric TBI.¹² Care included mechanical ventilation, elevation of the head of the bed to 30°, sedation, seizure prophylaxis, and placement of an ICP monitor with CSF drainage if ventriculostomy was performed. Age-appropriate CPP (neonates ≥ 40 mm Hg, children 50–60 mm Hg, and adolescents > 60 mm Hg) was maintained using

fluid boluses and vasopressors if needed. Persistent elevation in ICP (≥ 20 mm Hg), despite these therapies, was treated with the institution of paralytics and hyperosmolar therapy. Hyperventilation, barbiturate coma, and decompressive craniectomy were used for refractory elevations in ICP.

CO₂R Testing

Transcranial Doppler ultrasonography (TCD) was performed at the patient's bedside by 1 of 2 sonographers using a 2-MHz pulsed probe and commercially available TCD ultrasonography unit (Sonara Digital TCD; CareFusion). Training sessions prior to this study were performed to ensure a $< 10\%$ coefficient of variation in measurements between sonographers. Initial TCD recordings were performed within 24 hours of the injury, and daily examinations were done thereafter. The clinical care team was blinded to the findings of the TCD examinations. All studies, including those obtained from patients who were nearing brain death, were included in the analysis.

The end-tidal CO₂ (ETCO₂) concentration was monitored in all patients. CO₂R was tested using previously described methods.^{8,11} Testing was performed only in intubated patients who could have their ETCO₂ decreased by at least 5 mm Hg and were hemodynamically stable. Minute ventilation was transiently increased by altering the respiratory rate while ETCO₂ was monitored. The mean blood flow velocity of the right and left middle cerebral arteries (V_{MCA}) was evaluated at baseline and then immediately again after ETCO₂ had decreased by at least 5 mm Hg and remained stable for more than 2 minutes in order to achieve steady-state conditions.¹⁰ Heart rate, mean blood pressure, and body temperature remained unchanged throughout the study period. Relative CO₂R was determined by calculating the ratio of percent change in V_{MCA} per mm Hg change in ETCO₂ ($\% \Delta V_{MCA} / \text{mm Hg}$).¹¹ CO₂R testing was not performed on days when the patient already had an ETCO₂ less than 35 mm Hg in order to prevent any additional harm from hypoperfusion and secondary ischemia from vasoconstriction. A normal range of CO₂R in children anesthetized with propofol has previously been defined as 10.3% to 13.8%.¹⁰

Clinical Outcome

Short-term outcome was assessed at the time of discharge from the hospital and again at 3 months after discharge using GOS-E Peds. This provides an age-appropriate, valid measurement of neurological outcome for infants and children younger than age 18 years with TBI.⁴ The 8 categories in the scale are: 1) upper good recovery; 2) lower good recovery; 3) upper moderate disability; 4) lower moderate disability; 5) upper severe disability; 6) lower severe disability; 7) vegetative state; and 8) death. For this study, good neurological outcome was considered to be a GOS-E Peds score ≤ 4 , and a poor neurological outcome was considered to be a GOS-E Peds score of 5 to 8. The patient population was divided into 3 age groups— younger than 2 years, 2 to 5 years old, and older than 5 years—due to the different tests that were needed to accomplish formal neurodevelopmental assessment.

Statistical Analysis

For each variable studied, standard descriptive statistics were calculated, and distributions were examined to verify normality and equality of group variances; non-parametric procedures were implemented when either assumption was violated. Due to small sample numbers, all analyses were restricted to data obtained during the first 7 days. For continuous measures, 1-way ANOVA or the Kruskal-Wallis test was used to determine any overall age group differences; pairwise comparisons with the Tukey adjustment for multiplicity were used to further examine any statistically significant between-group effects. Differences in continuous measures between the moderate and severe TBI groups were assessed using the independent-samples t-test or Wilcoxon rank-sum test, as appropriate. All associations between categorical variables were examined using the Fisher's exact test. Receiver operator characteristic (ROC) curve analysis was performed to define a threshold value for predicting favorable versus unfavorable outcomes. The optimal value was determined by minimizing Youden's J statistic ($J = \text{sensitivity} + \text{specificity} - 1$). This cut-point value was used to define abnormal CO_2R for this study. Linear and generalized linear (binomial with a logit link function) mixed models were used to determine important predictors of mean CO_2R and abnormal CO_2R over time, respectively. To improve the stability and validity of the mixed models, patients for whom only 1 measurement was obtained were excluded. Interactions between each predictor variable and day of measurement were examined, as well as whether there were any univariate main effects on CO_2R . Important predictors of outcome were assessed using univariate ordinary least squares and logistic regression models. A 2-sided probability level of less than 5% ($p < 0.05$) was considered significant. All analyses were performed using SAS (version 9.3; SAS Institute).

Results

Thirty-eight children (age range 1 day to 15.5 years) who were receiving mechanical ventilation following moderate or severe head trauma were included. The cohort included 28 male and 10 female patients. Seven patients underwent decompressive craniotomy upon admission, and this had no relationship with hemispheric or global CO_2R ($p = 0.8$). One patient was treated with barbiturate coma for fulminant, refractory intracranial hypertension. The patient population was divided into 3 age groups: under 2 years old ($n = 12$; 31%), 2 to 5 years old ($n = 9$; 24%), and older than 5 years ($n = 17$; 45%). Table 1 shows the descriptive statistics by age group. Those patients with severe TBI ($n = 30$) were evenly split between 5 years or younger and older than 5 years old.

Prevalence Of Abnormal CO_2R Over Time By Age and Sex

Based on the ROC curve analysis, a cut-point value of 2.7% was determined to be the threshold CO_2R value that was most predictive of poor outcome across all ages. Thus, a CO_2R value $< 2.7\%$ was considered to be abnormal, and this is consistent with the values used in previous studies.^{21,22} In the entire cohort, the majority of patients (53%)

TABLE 1. Descriptive statistics by age group

Variable	<2 Yrs Old				2–5 Yrs Old				>5 Yrs Old				p Value*
	No. of Patients	Mean (SD)	Median (IQR)	Range	No. of Patients	Mean (SD)	Median (IQR)	Range	No. of Patients	Mean (SD)	Median (IQR)	Range	
Age, yrs	12	0.5 (0.53)	0.33 (0.18–0.56)	0.01–1.71	9	3.99 (0.60)	4.11 (3.84–4.39)	3.1–4.91	17	10.65 (3.14)	10.29 (8.5–12.83)	5–15.5	
GCS score	12	8.5 (2.20)	8.5 (2.26–3.94)	5–12	9	7.22 (1.30)	7 (6–8)	6–9	17	6.76 (1.75)	7 (6–8)	3–10	0.05
Mean CO ₂ R, %	12	3.23 (3.55)	3.55 (2.26–3.94)	1.55–4.67	9	4.77 (0.96)	4.48 (4.36–5.41)	3.3–6.58	17	3.76 (1.28)	3.5 (2.63–4.64)	2.23–6.7	0.016
Maximum CO ₂ R, %	12	3.63 (1.22)	3.8 (2.73–4.65)	1.55–5.4	9	7.07 (2.97)	6.3 (4.36–5.41)	4.25–13.5	17	4.92 (2.05)	4 (3.3–6.5)	2.25–8.55	0.003
Minimum CO ₂ R, %	12	2.82 (1.16)	3.18 (1.81–3.68)	0.70–4.5	9	3.14 (1.58)	2.85 (2.05–4.25)	1.44–6.35	17	2.55 (1.28)	2.25 (1.95–3.15)	0.08–5.9	0.554
Proportion abnormal†	12	0.33 (0.45)	0 (0–0.83)	0–1	9	0.21 (0.22)	0.2 (0–0.4)	0–0.5	17	0.29 (0.33)	0.33 (0–0.5)	0–1	0.857
Mean ICP, mm Hg‡	2	8.43 (0.61)	8.43 (8–8.86)	8–8.86	5	12.3 (3.22)	11.33 (9.57–15)	9.14–16.3	11	12.3 (6.69)	10.75 (8–13.67)	4–28.3	0.284
DC GOS-E score	12	4.25 (2.45)	5.5 (1–6)	1–7	9	5.22 (2.49)	6 (5–7)	1–7	17	4.59 (2.12)	5 (4–6)	1–7	0.387
3-mo GOS-E score	12	3.83 (2.29)	5 (1–5.5)	1–7	8	4.13 (2.47)	4 (2–6.5)	1–7	17	3.06 (2.01)	3 (1.4)	1–7	0.485

DC = discharge; IQR = interquartile range.

* Boldface type indicates statistical significance.

† Indicates the percentage of patients with abnormal CO_2R measurements.

‡ Only some patients had an ICP monitor placed.

had an abnormal mean CO₂R for greater than 20% of their measurements. Those with severe TBI had impaired CO₂R for 35% of the time compared with 10% for those with moderate TBI (22 severe and 9 moderate TBI patients) ($p = 0.029$). Thirty-one patients (22 severe and 9 moderate TBI patients) were able to complete CO₂R testing during the first 48 hours of admission, and, of these, 68% had impaired CO₂R in at least 1 hemisphere during this time.

In the entire cohort, CO₂R tended to improve over time. By Postinjury Day (PID) 3 to 4, nearly all patients had normalized their CO₂R. Of the 16 patients intubated longer than 4 days, 4 patients had impaired global CO₂R values after this time point (Fig. 1). These patients who had abnormal CO₂R later in their hospital course were intubated for longer ($p = 0.016$), had lower minimum CO₂R values ($p = 0.047$), and a greater proportion of impaired CO₂R measurements than those whose CO₂R remained steady or increased.

Children in the youngest age category (< 2 years) had a lower mean CO₂R over time (Fig. 2). The 2–5-year-old age group had both significantly higher mean CO₂R than the younger patients ($p = 0.016$) and greater maximum CO₂R than either of the other age groups ($p = 0.003$) (Table 1). Male patients initially had lower mean CO₂R than female patients (Fig. 3). By PID 6, this relationship reverses. In those children with severe TBI, the effect of sex on CO₂R over time is significant ($p = 0.019$) and trends toward significance in those children with moderate TBI ($p = 0.067$).

Predictors of Abnormal CO₂R

No variables that we evaluated (age, GCS score, ICP, Injury Severity Score, sex, MOI) were associated with an abnormal CO₂R.

Outcome Correlation

We found a statistically significant effect of the minimum recorded CO₂R on the GOS-E Peds score at hospital discharge. On average, a 1-percentile increase in minimum CO₂R decreases GOS-E Peds at discharge by 0.58 points ($p = 0.041$). The proportion of abnormal mean CO₂R values trends toward having a significant effect on the outcome score at discharge ($p = 0.104$). Of the 12 patients who had an abnormal CO₂R value in either hemisphere after 48 hours postinjury, all but 1 patient had poor neurological outcomes at discharge. Impaired CO₂R beyond PID 4 showed a near-significant association with outcome at discharge ($p = 0.086$).

Discussion

This is one of the few studies to describe CO₂R in pe-

FIG. 1. Proportion of patients with abnormal CO₂R over time.

FIG. 2. CO₂R over time by age group.

diatric age groups after the first 48 hours following TBI. Similar to other adult and pediatric studies, we found that it is common to have impaired CO₂R within the first 48 hours after injury,^{2,13,18} and there were wide variations in timing, location, and duration of this impairment.¹ Additionally, almost half of the patients who were still intubated after 48 hours had some impairment in either 1 or both hemispheres. There is a trend toward male patients initially having lower mean CO₂R than female patients, but this relationship switches after PID 6 (Fig. 3). Baseline differences exist in CO₂R and CBF between the sexes in healthy individuals,³⁰ and so the sex differences in CO₂R that we found in our cohort are not necessarily surprising. Similar to other studies, almost all our patients had normalized CO₂R by PID 3 to 4.^{8,13,18} However, there were some individuals who had a late-onset or the recurrence of impaired CO₂R after PID 4, which interestingly coincided with changes in clinical management (e.g., weaning of paralysis, sedation, and hyperosmolar therapy) or new imaging findings (e.g., carotid artery dissection and intracranial bleeding). All of these patients had poor GOS-E Peds scores at discharge. This suggests that the trend in CO₂R after 48 hours postinjury and/or while weaning off ICP-controlling therapies may provide valuable data. Because this is a pilot study, future larger investigations could examine if impaired CO₂R after 48 hours correlates with changes in management, new evolving injuries, and outcome.

Another aim of this study was to describe the patterns of impaired CO₂R over time in different pediatric age groups after TBI. In our study, we found that the 2–5-year-old age group had better preservation of CO₂R compared with either of the other age groups. Children in the youngest age category (< 2 years old) had lower mean CO₂R over time compared with the other age groups (Fig. 2). Adelson et al. conducted a retrospective chart review study in which 27 pediatric patients had CO₂ vasoreactivity evaluated using Xe CT in order to measure CBF measurements in response to PaCO₂ changes.² They found no correlation between age and impaired CO₂R; however, this patient population was divided into age groups that are different from the age groups used in our study (those younger than or older than 5 years), and CO₂R was typically assessed once within the first 48 hours after injury rather than daily.

The age-based variations in CO₂R over time that are evident in our patient population may be partly due to the diverse primary MOIs that result in the heterogeneity of brain damage. Some of our patients suffered abusive head trauma (AHT), and we had more of this MOI in

FIG. 3. CO₂R over time by sex.

our younger-than-2-year-old age group compared with the other groups. Infants with AHT can present with apnea, and CO₂R has been shown to be decreased and remain impaired after severe hypoxia.^{13,17,23} These abused patients may have also sustained repeated head trauma. However, we did not find a significant association between MOI and global mean CO₂R, which may be due to our small sample size. There were also no significant differences in global CO₂R over time between those patients who suffered AHT versus any other MOI ($p = 0.24$). Table 2 shows the mean CO₂R values by age group for each MOI. Additional studies with larger numbers of patients that are designed to evaluate the impact of MOI on CO₂R and outcome are needed. Multiple studies involving adult patients have shown a link between poor neurological outcomes and impaired CO₂R.^{8,13,19–21,28} One pediatric study found patients with higher mean CO₂R trended toward a more favorable outcome, and CO₂R < 2%/torr PaCO₂ in the first 48 hours after injury was correlated with poor neurological outcome at 6 months after injury.² Similar to that study, our patients trended toward having an association between impaired CO₂R in the first 48 hours after injury and poor neurological outcome at discharge. In our cohort, there was a significant relationship between the minimum recorded CO₂R values over time and poor outcome scores at hospital discharge.

Limitations

TCD is a noninvasive, portable procedure that can be performed at bedside, making it a useful tool for repeated measurements and following changes in cerebral circulation after head injury. TCD can provide accurate, reproducible measurements of CO₂R after TBI.¹¹ It allows for assessment of mean blood flow velocity in the major cerebral arteries, but this value is not interchangeable with CBF.²⁴ We observed impaired CO₂R in children after TBI, but it is unknown how this affected CBF in these patients.

There were several limitations to our study. This was a single-institution study with a relatively small sample size, and thus the results may not be generalizable. However, our sample size is similar to slightly larger than most other previously published CO₂R studies on pediatric TBI. Future studies should examine similar aims in larger cohorts of patients. Another limitation is that some of our sickest patients had missing data in the first 48 hours after injury due to tight PaCO₂ regulation by the clinical team, resulting in ETCO₂ < 35 mm Hg. We did not further hyperventilate these patients to prevent additional ischemia and brain injury. In other patients, we were unable to lower ETCO₂ with ventilator adjustments due to either concurrent lung injury or abnormal respiratory patterns, leading to ven-

TABLE 2. Mean global CO₂R values by age group and MOI

MOI	Mean (no. of patients)		
	<2 Yrs	2–5 Yrs	>5 Yrs
Fall	3.35 (3)		2.47 (1)
Motor vehicle accident		4.96 (6)	4.02 (5)
Pedestrian vs auto	3.91 (2)	4.25 (1)	3.51 (5)
AHT	2.97 (7)	4.78 (1)	3.38 (2)
Other*		4.45 (1)	4.06 (4)

* Other includes gunshot to head, all-terrain vehicle accident, and unknown.

tilator dyssynchrony. Statistical analyses were adjusted appropriately to account for missing data, but our results may still have underestimated the prevalence and association of impaired CO₂R on outcome.

Lastly, limited normative data for CO₂R in children exist. Karsli et al. evaluated healthy children who were anesthetized with propofol and found that CO₂R ranged from 10.3% to 13.8% over a wide range of ETCO₂ values (range 25–55 mm Hg).¹⁰ Other pediatric studies have found a value of < 2% in the first 48 hours after injury to be associated with poor neurological outcome.^{2,5} Based on the limited available data and ROC curve analysis of our data, we considered a threshold of < 2.7% as abnormal. Due to small patient numbers affecting the validity of results, we could not use regression models to generate age-specific thresholds.

Conclusions

Abnormal CO₂R is prevalent in children following TBI and can occur after the initial 48 hours postinjury. There are no obvious predictors that identify those who will have abnormal vasoreactivity. Lower minimum CO₂R values over time are associated with worse GOS-E Peds scores at hospital discharge.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Maa, Yeates, O'Brien. Acquisition of data: Maa, Yeates, O'Brien. Analysis and interpretation of data: all authors. Drafting the article: Maa, Moore-Clingenpeel, O'Brien. Critically revising the article: Maa, Moore-Clingenpeel, O'Brien. Reviewed submitted version of manuscript: Maa, Moore-Clingenpeel, O'Brien. Approved the final version of the manuscript on behalf of all authors: Maa. Statistical analysis: Moore-Clingenpeel, O'Brien. Administrative/technical/material support: O'Brien. Study supervision: Maa, Yeates, O'Brien.

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