OPEN

Cerebrovascular Pressure Reactivity Has a Strong and Independent Association With Outcome in Children With Severe Traumatic Brain Injury*

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OBJECTIVES: To examine cerebrovascular pressure reactivity index (PRx) in a large cohort of children with severe traumatic brain injury (sTBI) in association with physiologic variables and outcome.

DESIGN: Retrospective observational cohort study.

SETTING: Red Cross War Memorial Children's Hospital in Cape Town, South Africa.

PATIENTS: Pediatric (≤ 14 yr old) sTBI patients with intracranial pressure (ICP) monitoring (postresuscitation Glasgow Coma Score [Glasgow Coma Scale (GCS)] of ≤ 8).

MEASUREMENTS AND MAIN RESULTS: Data were analyzed from ICM+ files sampled at 100Hz. PRx (a mathematical indicator of pressure reactivity) was calculated as a moving correlation coefficient between ICP and mean arterial pressure (MAP) as previously described. Associations between PRx, age, GCS, ICP, MAP, and cerebral perfusion pressure (CPP) were examined with summary measures and correlation analysis using high-frequency data. Associations between PRx and mortality/outcome were examined with multivariable logistic regression analysis and the prognostic ability of PRx with receiver operating characteristic (ROCs) curves. The dataset included over 1.7 million minutes (28,634 hr) of MAP and ICP data in 196 children. The series mortality was 10.7% (21/196), and unfavorable outcome 29.6% (58/196). PRx had a moderate positive correlation with ICP ($r = 0.44$; $p < 0.001$), a moderate negative correlation with CPP ($r = -0.43$; $p < 0.001$), and a weak negative correlation with MAP ($r = -0.21$; $p = 0.004$). PRx was consistently higher in patients with poor outcome and had a strong, independent association with mortality (ROC area under the curve = 0.91). A PRx threshold of 0.25 showed the best predictive ability for mortality.

CONCLUSIONS: This is the largest cohort of children with PRx analysis of cerebrovascular reactivity to date. PRx had a strong association with outcome that was independent of ICP, CPP, GCS, and age. The data suggest that impaired autoregulation is an independent factor associated with poor outcome and may be useful in directing clinical care.

KEY WORDS: autoregulation; cerebral blood flow; cerebrovascular pressure reactivity; children; critical care; traumatic brain injury

Severe traumatic brain injury (sTBI) is a leading cause of morbidity and mortality in children across the globe. However, there are very few high-level recommendations in evidence-based guidelines due to lack of data. Pediatric-specific studies are less common because children are considered a vulnerable population in research, and most centers have less experience with pediatric sTBI than adult sTBI. Although blood pressure management is

***See also p. 680.**

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KEY POINTS

Question: The goal of this study was to describe PRx, the pressure reactivity index, in a large cohort of children with severe traumatic brain injury (sTBI) and to examine its association with key intracranial variables and outcome.

Findings: This retrospective study of 196 children with sTBI found that PRx has a strong and independent association with mortality, with a PRx threshold of 0.25 showing best discrimination.

Meaning: Impaired pressure reactivity is independently associated with poor outcome in pediatrics, and hence PRx may be important in clinical care of children with sTBI.

critical in sTBI care, the recommendations guiding its management in pediatric sTBI are weak, and autoregulatory status is usually not reported in clinical studies or factored into clinical decision-making.

This is important because cerebral autoregulation (CA) is a physiologic mechanism that maintains cerebral blood flow across a range of systemic blood pressures. Cerebrovascular pressure reactivity is a distinct component of CA and relates to the ability of smooth vascular cells to react to changes in transmural pressure (1).

CA is not commonly assessed in most centers, and testing does not form part of current recommendations, presumably in part because of the difficulty in testing. The assessment of CA status requires mean arterial pressure (MAP) and a measure of cerebral blood volume, or a proxy thereof. Currently, there are static and dynamic measurements of CA (2). Static readings can be calculated using the administration of drugs that alter MAP without changing metabolism. However, these require provocative tests such as raising or lowering the blood pressure while monitoring transcranial Doppler cerebral blood flow velocities to measure the response in vascular resistance. These tests are invasive, time consuming, and technique dependent. Dynamic measurements may be more clinically useful as they take time into consideration, and this allows for continuous patient monitoring. One dynamic measurement of cerebrovascular pressure reactivity is PRx, the pressure reactivity index. PRx is arguably the most widely used indication of the status of pressure reactivity in research studies; but there are few studies in children, and the cohort sizes are small, the largest to date consisting of 56 patients (3–8). It is essential to develop robust pediatric-specific data because children have different physiologic blood pressure ranges across the age continuum, different baseline cerebral blood flow ranges, different cerebrovascular responses to stimuli (9–11), and different injury patterns. Current guidelines for children have no recommendation on how to factor CA status into clinical practice (12), but this has been recently introduced for adult TBI (13).

Because the CA status may have important implications on managing blood pressure in pediatric sTBI, we aimed to examine the characteristics of PRx in a large cohort of children with sTBI. Our objectives were to examine associations between PRx and clinical variables and to examine associations between PRx and outcome.

MATERIALS AND METHODS

Patient Selection

Analysis was performed on prospectively collected high-frequency data of children with sTBI who underwent clinically indicated ICP monitoring at the Red Cross War Memorial Children's Hospital. Consecutive patients were included in this study if continuous recordings of intracranial pressure (ICP) and MAP were available and if there was at least 24 cumulative hours within the first 3 days of monitoring for which PRx could be calculated (see **Supplementary Data**, http://links.lww.com/CCM/H287, for more details).

Clinical Management

Patients were managed in keeping with management guidelines for children with sTBI (12, 14) but adapted to a local protocol (15). Broadly, initial targets for treatment were as follows: ICP less than or equal to 20 mm Hg (or 15 mm Hg in children 2 yr old or younger), cerebral perfusion pressure (CPP) greater than or equal to 50 mm Hg (or 40–45 mm Hg in children 2 yr or younger), and brain tissue oxygenation ($Pbto_2$) greater than or equal to 20 mm Hg (10 mm Hg hard threshold). Therapy thresholds were then titrated based on clinical

course, interaction between variables, and response to therapy. See **Supplementary Text** (http://links.lww.com/CCM/H287) for more details of the clinical protocols of care.

Data Recording and Collection

ICP was monitored using an intraparenchymal catheter (CODMAN ICP EXPRESS, Integra Life Sciences, Princeton, NJ); CPP was mathematically calculated as MAP-ICP. All physiological data were collected in real-time at the bedside using the computerized recording system ICM+ (Cambridge University, Cambridge, United Kingdom) at a frequency of 100 Hz.

The primary endpoint was mortality at 6 months. Clinical outcome at greater than or equal to 6 months post injury was based on the eight-point Pediatric Glasgow Outcome Scale Extended (GOS-E) version (16). This was dichotomized as favorable (1–4) and unfavorable (5–8) outcome groups.

Data Analysis

PRx Calculation. Manual data cleaning and artifact removal were performed in the raw files of ICM+. PRx was calculated in ICM+ as the moving Pearson correlation coefficient between 30 consecutive 10-second averaged data points of ICP and MAP (5, 17). One-minute averages of all variables were calculated for the entire cohort. Single descriptive values of each variable for each individual patient were calculated from this minute-by-minute data. Further, to derive hourly data points for each patient, minute-by-minute data were averaged for every hour or part thereof.

The following metrics were collected for analysis: an average data point per hour, a single median value for each patient's entire monitoring period, and a median PRx per day. PRx ranges between –1 and 1, with higher PRx values associated with weaker vascular reactivity response. To examine discriminative thresholds of PRx, we examined the percentage time spent with a PRx above 0, 0.2, 0.25, and 0.3. To examine potential confounding of increased ICP in biasing the calculation of PRx, we also calculated the median PRx per patient when hourly ICP was less than or equal to 20 mm Hg. The percentage of time that patients spent with an ICP above 20 mm Hg, and the median PRx across a range of CPP values, was calculated.

To Describe the Characteristics of PRx in Children With sTBI. Demographic, clinical, and outcome data were collected. To investigate the changes in PRx over time, the median hourly PRx for each monitoring day was plotted by outcome groups. Clinical outcome was analyzed in three ways: 1) primary endpoint mortality at 6 months post injury, 2) secondary endpoint dichotomized clinical outcome according to the GOS-E (16), and 3) functional outcome for survivors.

To Examine Associations Between PRx, Clinical, and Physiologic Variables. The relationship between PRx, ICP, MAP, and CPP was investigated with Spearman rank correlation analysis, using the overall median of each patient's entire monitoring period, that is, 196 data points were included for each variable. GCS and age were included in the analysis. To graphically demonstrate the relationship between overall PRx and CPP, CPP was calculated in bins of 10 mm Hg, against which median PRx was plotted.

To Examine Associations Between PRx and Outcome.

1) For univariate analysis, we used the Mann-Whitney's *U* test to examine differences in median PRx between outcome groups, and logistic regression (with PRx as the only predictor of outcome) and receiver operating characteristic (ROC) analyses to investigate the relationship between PRx and clinical outcome.
2) For multivariable logistic regression, ICP, CPP, GCS, and age were added to the model. We used the median PRx, ICP, and CPP for each patient (as continuous variables). PRx values were multiplied by 10 to enable meaningful interpretation of the resulting odds ratios (ORs) (5). The interaction between PRx and ICP (both continuous and at the threshold of 20 mm Hg) was investigated, but this relationship was not significant. Multicollinearity was assessed but there were no detectable concerns.
3) Using ROC analysis, we examined overall median PRx, ICP, and CPP, as well as the median percentage time spent above various PRx thresholds and above an ICP of 20 mm Hg, as predictors of death and unfavorable outcome. These variables were calculated using the hourly data—the number of hours PRx or ICP were above a given value divided by the entire period for which PRx or ICP data were available, reported as a percentage of time. The PRx threshold values of 0, 0.25, and 0.3 have previously been described in both adults (18–20) and children (5) as mortality thresholds. In the ROC analysis in 1) above, the PRx threshold of 0.2 was identified as having the best combination of sensitivity and specificity for mortality for this study's cohort (**Supplementary Fig. S4**, http://links.lww.com/CCM/H287) and was therefore used in further analysis. A further ROC analysis was performed to examine PRx when ICP was less than 20 mm Hg to control from the impact of raised ICP on outcome.

Statistical significance was set as p value of less than 0.05. All statistical analysis was done using IBM SPSS Statistics 27.0 (released 2020; IBM Corp, Armonk, NY). As this was an exploratory analysis, we did not account for multiple testing. Data collection and reporting were approved by the Human Research Ethics Committee of the University of Cape Town (HREC 166/2009—study title "Pediatric Critical Care," approved in 2009 with annual renewal), and procedures were followed in accordance with the standards of this committee, and the 1975 Helsinki Declaration. Informed consent was obtained from parents/legal guardians of the child.

RESULTS

One hundred ninety-six children with sTBI were included in analyses. Their ages ranged from 4 days to 14 years and were admitted between March 2009 and December 2019. The total monitoring time was over 1.7 million minutes (28,634 hr).

Demographic, Clinical, and Monitoring Data

Table 1 shows summary statistics for the entire cohort, separated into survivors (n = 175; 89.3%) and nonsurvivors (n = 21; 10.7%). For dichotomized outcome, 138 patients (70.4%) had a favorable outcome, and 58 (29.6%) had an unfavorable outcome (37 of whom survived). $Paco_2$ data were only available for a subset of patients (n = 75), the mean of which was 4.6 ± 1.1 kPa.

Temporal Profile of PRx

Survivors and patients with a favorable outcome had a consistently lower median PRx over 10 days of monitoring compared with nonsurvivors and patients with an unfavorable outcome, respectively (**Fig. 1**). This remained true for functional outcome when patients who died were excluded (**Supplementary Fig. S1**, http://links.lww.com/CCM/H287). Interpretation of data beyond days 8–10 was limited by the low number of data points (**Supplementary Fig. S2**, http://links.lww.com/CCM/H287).

The Relationship Between PRx and Clinical and Physiologic Variables

PRx and ICP were moderately positively correlated (r = 0.44; p < 0.001). PRx was negatively correlated with both CPP (r = –0.43; p < 0.001) and MAP (r = –0.21; p = 0.004). There were no significant correlations between PRx and age or postresuscitation GCS (**Supplementary Table S2**, http://links.lww.com/CCM/H287).

Figure 2 shows median PRx plotted against CPP bins. PRx was higher at low CPPs and gradually decreased as CPP increased, with PRx at its lowest of –0.04 corresponding to a CPP bin of 70–80 mm Hg, with only a modest rise thereafter. PRx versus CPP bins plotted for various age groups can be found in **Supplementary Figure S3** (http://links.lww.com/CCM/H287).

The Relationship Between PRx and Outcome

The overall median PRx was 0.00 for survivors and 0.37 for patients who died (p < 0.001) (Table 1). The percentage of time spent above each of the PRx thresholds (0, 0.2, 0.25, and 0.3) was greater in patients who died (p < 0.001 for all analyses). Nonsurvivors demonstrated a higher median ICP (19.2 vs 11.9 mm Hg for survivors; p < 0.001) and percentage time spent above an ICP of 20 mm Hg (44.2% vs 4.8%; p < 0.001). Median PRx (p < 0.001) and ICP (p < 0.001) were also higher in patients with unfavorable outcomes (Table 1).

When PRx was used as a single predictor variable for mortality, the OR was 1.87 (95% CI (CI) of 1.49–2.40; p < 0.001). When ICP, CPP, GCS, and age were added as covariables, the OR was 1.75 (95% CI 1.26–2.44; p = 0.001). Median PRx, ICP, and GCS were independently associated with mortality and dichotomized outcome (**Table 2**). Median PRx used as single variable in regression analysis for dichotomized outcome results in an OR of 1.42 (05% CI 1.23–1.63; p < 0.001), but then decreased to 1.31 (1.09–1.57; p = 0.004) when ICP, CPP, GCS, and age were added as covariables. Multicollinearity between PRx, ICP, and CPP was assessed, but there were no detectable concerns so no further investigations were done. Interactions between ICP and PRx were considered, but this relationship was found to be nonsignificant for all outcomes, and so it was not analyzed further.

The area under the curve (AUC) for mortality for median PRx was 0.91 (95% CI 0.86–0.96), for ICP 0.86 (95% CI 0.74–0.97), and for CPP 0.76 (95% CI 0.63–0.89). For the percentage time above PRx thresholds, the highest AUC value was for the 0.25 threshold. When hourly ICP was less than 20 mm Hg, PRx had an AUC of 0.90 (95% CI 0.85–0.96) for mortality. The median percentage time ICP was above 20 mm Hg showed an AUC of 0.94 (95% CI 0.89–0.99) (summary

TABLE 1.
Demographic, Clinical, and Monitoring Data for the Entire Cohort and Outcome Groups

Variables	Entire Cohort	Survivors	Nonsurvivors	*p*	Favorable	Unfavorable	*p*
Total, *n* (%)	196	175 (89.3)	21 (10.7)		138 (70.4)	58 (29.6)	
Demographics							
Age, median, yr	6.7 (4.3–9.1)	6.6 (4.3–9.1)	7.1 (4.73–10.1)	0.396	6.6 (4.1–9.0)	6.9 (4.9–9.6)	0.407
Males, *n* (%)	131 (66.8)	118 (67.4)	13 (61.9)		93 (67.4)	38 (65.5)	
Mechanism, *n* (%)							
Motor vehicle collision	50 (25.5)	46 (26.3)	4 (19.1)		33 (23.9)	17 (29.3)	
Pedestrian in motor vehicle collision	118 (60.2)	107 (61.1)	11 (52.4)		87 (63.0)	31 (53.5)	
Fall from height	8 (4.1)	5 (2.9)	3 (14.3)		4 (2.9)	4 (6.9)	
Gunshot wound to head	7 (3.6)	6 (3.4)	1 (4.8)		5 (3.6)	2 (3.5)	
Crush injury	6 (3.1)	6 (3.4)	0 (0.0)		6 (4.4)	0 (0.0)	
Any nonaccidental injury (including but not limited to abusive head trauma)	6 (3.1)	5 (2.9)	1 (4.8)		3 (2.2)	3 (5.2)	
Unknown	1 (0.5)	0 (0.0)	1 (4.8)		0 (0.0)	1 (1.7)	
Presentation							
Postresuscitation Glasgow Coma Score, median	6 (5–7)	6 (5–8)	5 (4–6)	**0.002**	7 (6–8)	6 (5–7)	**< 0.001**
Overall monitoring period							
Total monitoring time, d	5.1 (3.9–8.7)	5.1 (4.0–8.5)	4.2 (1.7–9.4)	0.264	4.9 (3.9–7.5)	8.3 (3.3–11.0)	0.006
ICP, median, mm Hg	12.4 (9.6–15.3)	11.9 (9.1–14.3)	19.2 (16.3–23.5)	**< 0.001**	11.4 (8.7–13.8)	14.4 (12.2–17.8)	**< 0.001**
ICP > 20 (median % time)	6.6 (0.0–18.4)	4.8 (0.0–13.2)	44.2 (25.6–78.5)	**< 0.001**	3.7 (0.0–11.0)	20.5 (6.2–34.4)	**< 0.001**
Mean arterial pressure, median, mm Hg	80.0 (74.0–85.6)	80.3 (74.0–85.6)	77.8 (72.6–89.7)	0.599	80.2 (74.1–85.6)	79.3 (73.8–85.4)	0.624
Cerebral perfusion pressure, median, mm Hg	67.7 (60.2–73.5)	68.2 (60.9–73.6)	58.1 (48.2–66.0)	**< 0.001**	68.3 (61.2–74.0)	63.2 (56.1–70.5)	**0.002**
PRx, median	0.01 (-0.12–0.20)	0.00 (-0.14–0.12)	0.37 (0.26–0.61)	**< 0.001**	-0.03 (-0.15–0.11)	0.16 (0.01–0.37)	**< 0.001**
PRx > 0 (median % time)	55.3 (34.6–74.0)	49.7 (32.1–67.8)	84.1 (77.9–99.1)	**< 0.001**	46.5 (30.5–67.3)	63.6 (51.1–88.9)	**< 0.001**
PRx > 0.2 (median % time)	25.0 (11.8–44.1)	22.3 (11.1–38.4)	62.0 (48.3–86.9)	**< 0.001**	19.5 (10.6–36.2)	42.0 (23.3–65.3)	**< 0.001**
PRx > 0.25 (median % time)	19.5 (9.0–37.8)	16.3 (7.2–31.7)	59.3 (43.8–87.9)	**< 0.001**	14.1 (7.0–28.6)	35.7 (20.1–59.6)	**< 0.001**
PRx > 0.3 (median % time)	15.2 (6.0–33.3)	13.2 (5.2–23.5)	54.0 (36.9–86.0)	**< 0.001**	9.6 (4.7–21.8)	28.4 (15.0–54.0)	**< 0.001**

ICP = intracranial pressure, PRx = pressure reactivity index.

Medians reported with 25th and 75th percentiles in brackets. Percentage time calculated using hourly data. All numbers rounded to one decimal place except for PRx and *p* values. Boldface values indicate statistical significance between mortality groups at the 0.05 level. Further details of the cohort's presentation (focal neurologic deficits, secondary insults) and other surgeries can be found in **Supplementary Table S1** (http://links.lww.com/CCM/H287).

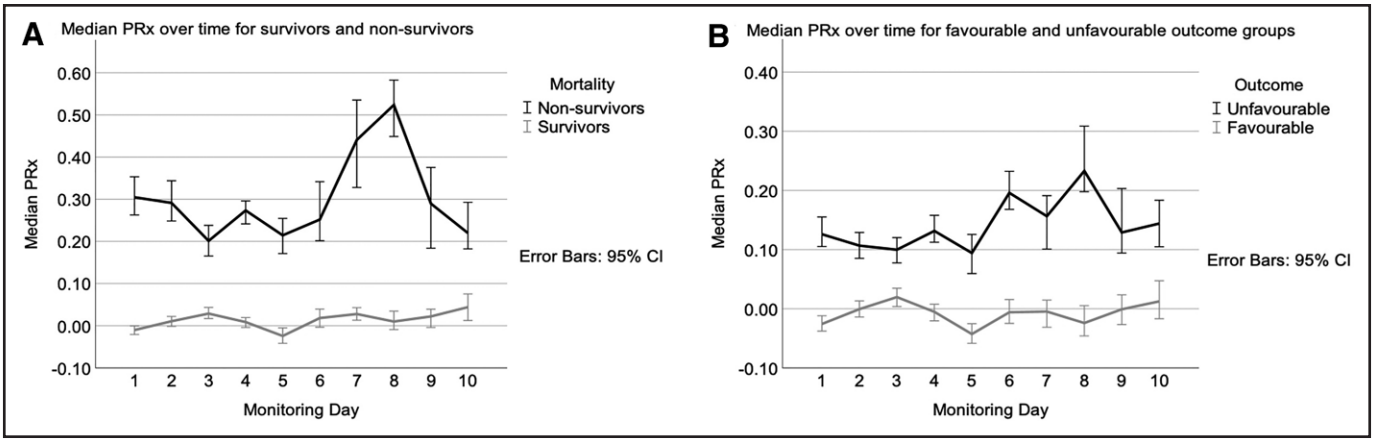

Figure 1. The temporal profiles of pressure reactivity index (PRx) by outcome groups. Median PRx plotted for the first 10 d of monitoring (due to adequate patient numbers per day—see Supplementary Fig. S2, http://links.lww.com/CCM/H287). Nonsurvivors = 21 patients, survivors = 175 patients, unfavorable = 58 patients, favorable = 138 patients. Glasgow Outcome Score Extended version scores for the groups as follows: favorable outcome = 1–4, unfavorable outcome = 5–8, error bars represent the 95% CI.

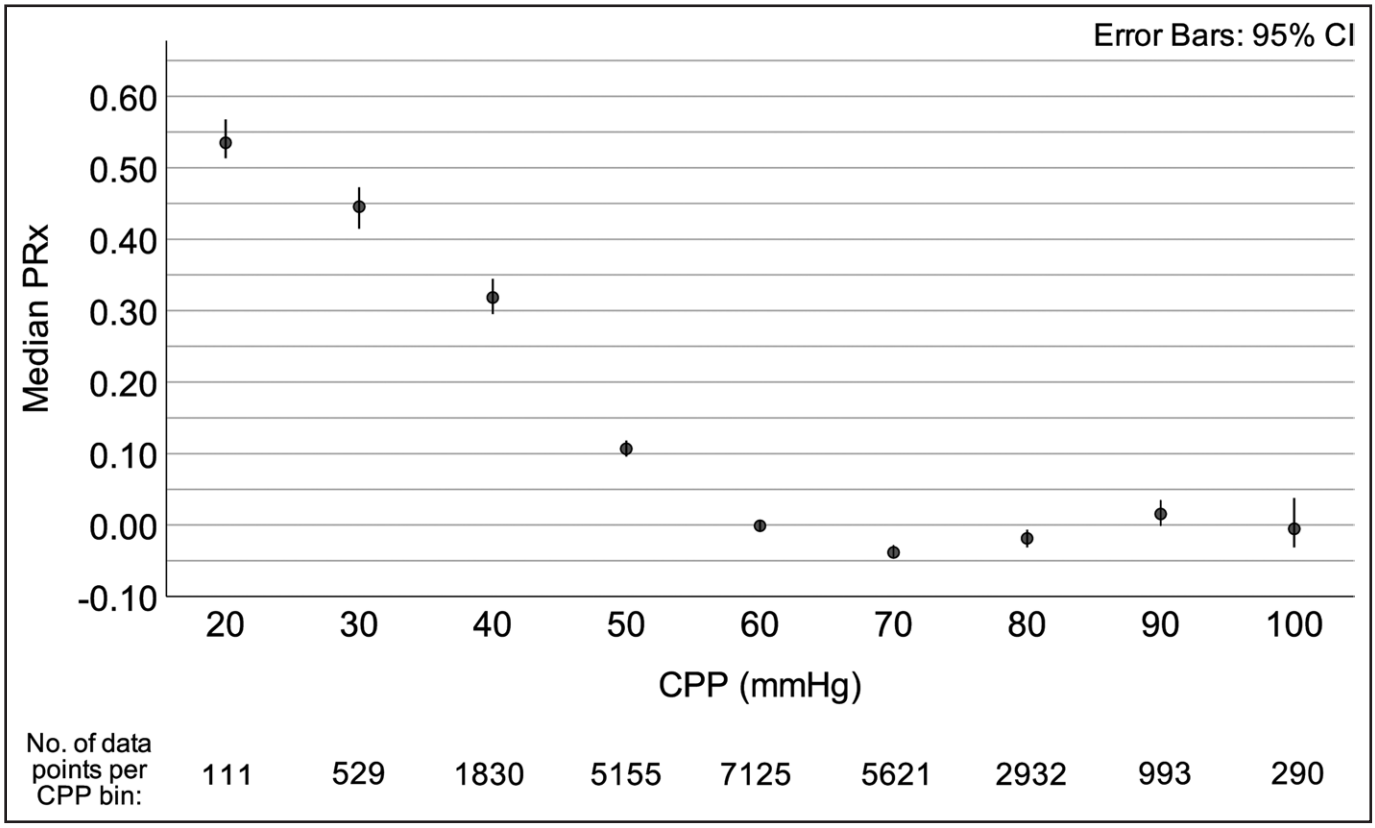

Figure 2. Median pressure reactivity index (PRx) versus cerebral perfusion pressure (CPP). Median PRx in 10 mm Hg CPP bins for the entire 196-patient cohort, with the number of data points included in each bin reported. See Supplementary Figure S3 (http://links.lww.com/CCM/H287) for median PRx versus CPP plotted for three distinct age groups (0–2 yr, 2–8 yr, > 8 yr old). Error bars represent the 95% CI.

in **Table 3**) (ROC curves in **Supplementary Figs. S4** and **S5**, http://links.lww.com/CCM/H287).

The AUC analyses were repeated for "unfavorable outcome," and summary results are shown in Table 3. In general, all AUC values were lower for unfavorable outcome compared with mortality.

DISCUSSION

There is a paucity of data on PRx, a mathematical indicator of the pressure reactivity component of CA, in children, with studies typically consisting of small cohorts (3–8). This study addresses that by describing

TABLE 2.
Logistic Regression Analysis for PRx and the Various Outcome Groups

Variables Analyzed	OR	95% CI	*p*
PRx and mortality			
PRx as single predictor			
Median PRx	1.87	1.49–2.40	**< 0.001**
Analysis with covariables			
Median PRx	1.75	1.26–2.44	**0.001**
Median ICP	1.24	1.01–1.51	**0.036**
Median CPP	0.99	0.92–1.07	0.852
GCS	0.63	0.43–0.91	**0.015**
Age	1.18	0.94–1.47	0.148
PRx and dichotomized outcome			
PRx as single predictor			
Median PRx	1.42	1.23–1.63	**< 0.001**
Analysis with covariables			
Median PRx	1.31	1.09–1.57	**0.004**
Median ICP	1.14	1.02–1.27	**0.025**
Median CPP	0.99	0.95–1.04	0.794
GCS	0.72	0.59–0.89	**0.002**
Age	1.09	0.96–1.23	0.191
PRx and functional outcome			
PRx as single predictor			
Median PRx	1.19	1.01–1.41	**0.034**
Analysis with covariables			
Median PRx	1.18	0.97–1.43	0.100
Median ICP	1.11	0.97–1.25	0.123
Median CPP	0.99	0.94–1.04	0.698
GCS	0.77	0.62–0.96	**0.018**
Age	1.07	0.93–1.22	0.337

CPP = cerebral perfusion pressure, GCS = postresuscitation Glasgow Coma Score, ICP = intracranial pressure, OR = odds ratio, PRx = pressure reactivity index.

Binary logistic regression analysis done for PRx and mortality, PRx and dichotomized outcome, and PRx and functional outcome (excluding deceased patients). The table reports results of median PRx as a single predictor, and median ICP, CPP, and GCS as covariable predictors of mortality/outcome. Median values per patient were used as a continuous variable for regression analysis. GCS analysis excluded one patient from the cohort ($n = 195$) because of uncertainty about the postresuscitation score. All numbers rounded to two decimal places, except *p* values. Boldface values indicate significance at the 0.05 level.

PRx in 196 children with sTBI. We examined its temporal profile, relationship with key clinical and physiologic variables, and association with outcome. The key findings of this study are as follows: 1) PRx was consistently higher in patients with poor outcome when examined by various summary statistics and over time, 2) PRx had a moderate correlation with ICP (positive) and CPP (negative); 3) PRx and ICP were strong independent predictors of outcome, and 4) the PRx threshold of 0.25 had the best predictive ability for mortality.

There was no significant relationship between the overall median PRx and GCS ($r = -0.09$; $p = 0.191$). This finding is supported by results in adult sTBI (21,

TABLE 3.
Comparing Area Under Curve Values From the Receiver Operating Characteristic Tests for the Various Outcome Groups

Tested Predictor	Area Under Curve Values Produced When Predicting		
	Mortality	Unfavorable	Poor Functional
Patient number	21	58	37
Median PRx	0.91	0.72	0.60
Median ICP	0.86	0.73	0.65
Median CPP	0.76	0.64	0.57
Median % time PRx > thresholds of			
0	0.90	–	–
0.2	0.87	–	–
0.25	0.91	–	–
0.3	0.90	–	–
Overall median ICP ≤ 20 mm Hg			
Median PRx	0.87	0.67	–
Median ICP	0.73	0.67	–
Median PRx when ICP ≤ 20 mm Hg	0.90	0.71	–
Median % time ICP > 20 mm Hg	0.94	0.76	–

ICP = intracranial pressure, PRx = pressure reactivity index.

Receiver operating curve analysis was done for mortality, unfavorable outcome, and poor functional outcome groups (survivors only). Percentage time variables calculated using the hourly data. Time spent above PRx thresholds evaluated for mortality groups only; analysis done for functional outcome with overall median PRx, ICP, and cerebral perfusion pressure tested only. To minimize multiple testing, analysis was done with all predictors for mortality, but only specific predictors were tested for unfavourable and poor functional outcome. All numbers rounded to two decimal places.

22), suggesting that PRx is not merely a proxy for injury severity, which in addition to its independent association with outcome, suggests it may represent a potential secondary injury mechanism that could be targeted. However, further analysis incorporating other markers of injury severity and radiological findings is needed.

Adult sTBI studies have shown a *U*-shaped curve when PRx is plotted against CPP (21, 22). Some centers use the lowest PRx value to describe an optimal CPP value, or CPPopt. We calculated PRx over a range of CPP values (Fig. 2) and demonstrated an expected gradual increase in PRx for low CPP. However, in the upper range of CPP, the increase in PRx was modest, suggesting relatively preserved vascular reactivity at higher CPPs, which is consistent with an autoregulatory plateau. A rise of PRx at higher CPP values may have occurred at even higher CPP values than occurred spontaneously in this cohort. Our finding is similar to that of Brady et al (4) as their PRx versus 5 mm Hg CPP bins showed lower values of PRx at the upper bins of CPP—pressure reactivity was intact at CPPs as high as 100 mm Hg. However, our study differed from that of Brady et al (4) as we plotted median PRx per CPP bin using the entire hourly dataset, whereas that group plotted PRx per CPP bin for each individual patient and then averaged these plots to create an overall mean of means, where equal weight was assigned to each patient. Although this may impact CPPopt calculations, the overall trend between PRx and CPP seems to be consistent. In contrast, Lewis et al (5) showed a *U*-shaped curve with PRx plotted against CPP in a smaller cohort. It is worth noting that different therapeutic strategies may potentially influence these findings.

Adult studies have demonstrated this signature *U*-shaped curve and have found that pressure reactivity deteriorates at a CPP below 60 mm Hg and above 80 mm Hg (22). However, it is possible that pressure reactivity is different in children. Some caveats are

important. First, the purpose of this specific analysis was to depict the relationship between PRx and CPP, not to calculate or treat CPPopt. Therefore, methodological steps of CPPopt calculation were not followed, and all PRx values were included in the CPP bin calculation, even if it included less than 2.5% of the total dataset (21). Second, this analysis summarizes the entire cohort's dataset, and individual PRx-CPP relationship curves may look different. Third, our institutional strategy does not target higher CPP thresholds, if the 45–50 mm Hg threshold for children is met and if $Pbto_2$ is acceptable (23). Therefore, the higher CPP range in this cohort does not reflect induced hypertension. Finally, further analysis is needed to investigate this PRx-CPP relationship across a range of ages in children. The median age of our cohort was 6.63 years old with a range of 4 days to 14 years old. Studies that include adolescent populations may produce different results more similar to adults, and very young patients may demonstrate different pathophysiology. Even though we did not demonstrate an association between PRx and age, this may require a larger cohort, especially for very young patients.

A PRx below 0 is considered intact, and values above 0.25 are thought to represent disturbed pressure reactivity (18). The pooled median PRx of this 196-patient cohort was 0.01. Overall, patients who had a favorable outcome had PRx values that fell within the intact pressure reactivity range over the duration of monitoring, whereas most of the elevated PRx values occurred in patients who had an unfavorable outcome. Further, nonsurvivors had a median PRx consistently above 0.2, and their impaired PRx persisted for a protracted time. This confirms the findings of smaller pediatric studies showing an association between PRx and outcome (3, 6). Furthermore, our results showed that PRx is associated with worse functional outcome in survivors and retained its association with outcome even when ICP was normal.

In the ROC analysis, median PRx had a predictive ability at least as strong as ICP. CPP had the weakest predictive ability. Median time spent above the investigated PRx thresholds all showed strong predictive abilities, with all AUC values being above 0.86, thus suggesting that PRx may have a dose-dependent effect on mortality prediction. The effect of PRx appears to be independent of ICP and so may represent a physiologic variable that may be used in clinical care.

LIMITATIONS

PRx is an "indicator" of pressure reactivity, and not a direct measurement, and is an inherently noisy signal, which may be affected by several variables that influence ICP and MAP. Using a single summary measure for the entire patient's monitoring period may have limited our findings, as well as those of other published studies. This was partly addressed in this study by analyzing time spent above threshold values. In addition, dichotomized outcome was used instead individual GOS-E score categories. Larger age-related cohorts would be needed for a finer categorical analysis. Radiologic findings on brain imaging were not included in this study due to the complexity of classification, especially in pediatric sTBI, for which there is no established classification. In addition, the effect of medication and surgical intervention (e.g., decompressive craniectomy surgery) was not included in the analysis. Limited data on withdrawal of life-sustaining therapies in deceased patients were available; however, given that the status of autoregulation does not influence the decision to withdraw therapy and that monitoring data is also censored at this point, we do not think that this would affect the relationship between autoregulatory status and outcome.

Importantly, we recognize that differences in mechanisms of injury, and age distribution vary across treatment centers. Finally, multiple testing was not controlled for in this analysis; however, the purpose of this study was to produce hypothesis-generating data, on which future pediatric studies can be based.

CONCLUSIONS

In this study, the largest of its kind in children, we have demonstrated that PRx is independently associated with clinical outcome in pediatric sTBI and that impaired PRx may be prolonged, at least over the first week of injury. PRx is typically deranged at low CPPs but relatively preserved at the upper range of spontaneously occurring CPP values in children. PRx may be a valuable prognostic indicator and a physiologic variable that should be incorporated into standard monitoring to direct clinical care. Integrating this, and how to apply it to children of different ages, needs further evaluation.

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All authors contributed to the conception and design of the study. Material preparation and data collection were done by Ms. Smith, Drs. Hina, Thango, Salie, and Enslin, and Prof. Figaji. Data analyses were done by Ms. Smith, Drs. Rohlwink and Mauff, and Prof. Figaji. Ms. Smith wrote the initial article draft, and all authors contributed to subsequent editing. All authors read and approved the final article.

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