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Intracranial Hypertension and Cerebral Hypoperfusion in Children with Severe Traumatic Brain Injury: Thresholds and Burden in Accidental and Abusive Insults

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Abstract

Objective—The evidence to guide therapy in pediatric TBI is lacking, including insight into the ICP/CPP thresholds in abusive head trauma (AHT). We examined ICP/CPP thresholds and indices of ICP and CPP burden in relationship to outcome in severe TBI and in accidental and AHT cohorts.

Design—A prospective observational study.

Setting—PICU in a tertiary children's hospital.

Patients—Children <18y admitted to PICU with severe TBI and had ICP monitoring.

Measurements and Main Results—A pediatric TBI database was interrogated with 85 patients (18 AHT) enrolled. Hourly ICP and CPP (in mm Hg) were collated and compared to various thresholds. C-statistics for ICP and CPP data in the entire population were determined. Intracranial hypertension and cerebral hypoperfusion indices were formulated based on number of hours with ICP>20 and CPP<50, respectively. A secondary analysis was performed on accidental and AHT cohorts. All of these were compared with dichotomized 6 month GOS scores. The models with the number of hours with ICP>20 (C=0.641, 95% confidence interval: 0.523, 0.762) and CPP<45 (C=0.702, 95% confidence interval: 0.586, 0.805) had the best fits to discriminate outcome. Two factors were independently associated with a poor outcome, number of hours ICP>20 and AHT (OR=5.101, 95% CI: 1.571, 16.563). As the number of hours with ICP>20 increase by 1, the odds of a poor outcome increased by 4.6% (OR=1.046, 95% CI: 1.012, 1.082).

Thresholds did not differ between accidental vs. AHT. The intracranial hypertension and cerebral hypoperfusion indices were both associated with outcome.

Conclusion—The duration of hours of ICP>20 and CPP<45 best discriminated poor outcome. As the number of hours ICP>20 increase by 1, the odds of a poor outcome increased by 4.6%. Although AHT was strongly associated with unfavorable outcome, ICP/ CPP thresholds did not differ between accidental and AHT.

Keywords

traumatic brain injury; cerebral perfusion pressure; intracranial hypertension; intracranial pressure; children; pediatric neurocritical care

Introduction

Injuries are the leading cause of death in children, with traumatic brain injury (TBI) accounting for the majority of these events (1). According to the Centers for Disease Control and Prevention, there were ~7440 deaths of children <19 years of age due to TBI in 2007 (2). In our pediatric intensive care unit (PICU), 20.5% of all deaths over a 21 month period were due to TBI (3). A nationwide study conducted in 2000 showed that an estimated 50,658 hospitalizations in children 17 years and younger were associated with TBI. During this year pediatric TBI accounted for >\$1 billion in inpatient hospital costs. (4) Unfortunately therapies that have been shown to improve outcome in TBI are lacking despite the significant burden it poses. Moreover, abusive head trauma (AHT) is a unique problem in the field of pediatric TBI and has emerged as an increasing contributor to TBI cases in children (5).

Measurement and management of intracranial pressure (ICP) and cerebral perfusion pressure (CPP = mean arterial pressure [MAP] – ICP) have been mainstays of neurocritical care for decades. Evidence-based guidelines for the management of severe TBI for both adult and pediatric patients have recommended ICP/ CPP monitoring for severe TBI (defined as Glasgow Coma Scale [GCS] score $\leq$ 8), as well as suggesting therapeutic targets (6, 7). Specifically, a recommendation based on level 2 evidence was made that an ICP threshold of 15 – 25 mm Hg for adult TBI victims *should* be considered and a recommendation based on level 3 evidence that a CPP threshold of 50 – 70 mm Hg *may* be considered. For children, there is substantially less evidence available to generate such guidelines. Nevertheless, level 3 recommendations were made to support an ICP treatment threshold of 20 mm Hg and a CPP threshold greater than 40 mm Hg. Further evidence to support such thresholds is needed as some recent studies have challenged the utility of ICP management (8, 9).

Pediatric TBI poses a unique challenge because of the various mechanisms of injury, specifically the unique mechanism of AHT that is not seen in other populations. There are a paucity of data explicitly examining this population and the guidelines make no specific recommendations for therapy for this unique group (6). It has been theorized that as this group is mostly comprised of children <2y, they may have lower normal ICP given lower normal MAP; and perhaps targeting a lower ICP threshold would improve outcomes. Others, however, have suggested that because of the presence of a fontanel, ICP monitoring is not

warranted in this group. We sought to provide further insight into the relationship of ICP and CPP in this particular group of TBI patients, as well as in the accidental TBI population.

Over the past several years, novel quantification schemes for the burden of intracranial hypertension and cerebral hypoperfusion have been proposed. Venkatesh and colleagues described the intracranial hypertension index and cerebral hypoperfusion index in an effort to quantify the actual duration of these disturbances (10). These indices utilize established thresholds and the duration of time of the abnormality, instead of episodic points or mean values. However, these indices have not been thoroughly evaluated for children.

In an attempt to address these deficiencies, we interrogated our pediatric TBI database and hypothesized that children with greater durations of both intracranial hypertension and decreased CPP (based on a priori thresholds) would have unfavorable outcomes. Secondly, we hypothesize that there will be differences in the association of ICP and CPP thresholds with outcomes between children with accidental and AHT mechanisms. Finally, we hypothesized that an increased intracranial hypertension index and cerebral hypoperfusion index would be associated with unfavorable outcome in children with severe TBI.

Methods

We interrogated the Pediatric Neurotrauma Registry of the Children's Hospital of Pittsburgh. In this registry, children <18 years of age were eligible for entry into this database if they were admitted to the PICU after diagnosis of severe TBI (GCS score $\leq$ 8). Informed consent must be obtained to be enrolled in this database. All mechanisms of injury were included in the initial part of the analysis. As abusive head trauma may have pathophysiology distinct from accidental TBI, a secondary analysis separating these two diagnoses was performed. For this secondary analysis, children were considered to have suffered AHT when a medical diagnosis of AHT was made by members of the Child Advocacy Team of the University of Pittsburgh – all of whom were unaware of the analysis being presented in this manuscript. The Institutional Review Board of the University of Pittsburgh approved this study and informed consent was obtained for data collection.

At our institution, a clinical protocol consistent with published guidelines was followed throughout the study period (1999–2009), with details being recently published (11). Briefly, all children with severe TBI were transported to our level 1 trauma center and initial resuscitation was performed by our trauma team including personnel from the emergency department, pediatric surgery, and pediatric critical care. Once the initial stabilization was complete, the children underwent neurologic assessment and imaging to define their injuries. For any child with a post-resuscitation GCS score $\leq$ 8, ICP monitoring was performed at the discretion of the Neurosurgery Staff. Almost all children, except those who were deemed to have lethal injuries where ICP monitoring was deemed futile, underwent monitoring. Our protocol strongly encourages placement of both an externalized ventricular drain (EVD) and intraparenchymal catheter, when feasible, based on our recent report (11). EVDs were inserted by Neurosurgery staff and mechanically-zeroed at the level of the tragus. Intraparenchymal catheters were mechanically-zeroed in accordance with the manufacturer's

instructions (Codman, Raynham, MA). Neurosurgery staff determined the need for surgical procedures, including but not limited to decompression of mass lesions.

All children were mechanically ventilated and received hemodynamic support including crystalloids and/or vasopressors, as needed. Invasive monitoring of blood pressure was routinely used with arterial catheters, placed at the discretion of the Critical Care Medicine (CCM) staff. Arterial catheters were mechanically-zeroed at the phlebostatic axis located at the 4th intercostal space midaxillary, which approximates the right atrium. Children were positioned with their head midline and the head of the bed elevated to 30°. For ICP management, a tiered approach was used. Intracranial hypertension was defined as ICP ≥ 20 mm Hg for ≥ 5 min and was treated aggressively in a stepwise fashion. Treatments included administration of sedation, neuromuscular blockade, mild hyperventilation ($\text{PaCO}_2 \sim 35$ mm Hg), continuous CSF drainage, hyperosmolar therapy (mannitol and/or 3% saline) and barbiturates. Additional therapies, including institution of barbiturate coma, therapeutic hypothermia and decompressive surgery were considered by the Neurosurgery and CCM teams, as appropriate. Concomitantly, CPP was targeted to a level above age-related thresholds (> 50 mm Hg for children ≤ 2 y and > 60 mm Hg for children > 2 y). If CPP decreased below these thresholds as a result of intracranial hypertension (ICP > 20 mm Hg), then therapies to lower ICP, described above, were generally first attempted. On the other hand, if CPP decreased below these thresholds without intracranial hypertension, then maneuvers to raise MAP (fluid resuscitation, vasopressor support or other maneuvers) were generally administered. In some patients, both strategies were required.

The data collected for this study included demographics extracted from the medical record, physiologic data taken from hourly recordings entered into the medical record by the bedside nurse, and outcomes determined by clinical staff in follow-up clinic. As many children had both an intraparenchymal ICP monitor and EVD, there were hours with more than one ICP and CPP reading. For those hours, the highest ICP and lowest CPP value were used. The outcome data were determined at 6 months after TBI by using the Glasgow Outcomes Scale (GOS) score which was dichotomized for favorable [1–2] and unfavorable [3–5] outcomes.

From this database, the number of hours of ICP above certain thresholds (>14 , >20 , >30 mm Hg) and CPP below certain thresholds (<40 , <45 , <50 , <55 , <60 mm Hg) were determined. Mean (overall and daily) ICP and CPP were calculated for the first five days of monitoring, as the majority of children included in this study underwent monitoring for at least 5 days and could fully contribute to the analysis of the “dose” of ICP/ CPP derangements. The intracranial hypertension index ($[\# \text{ hours of ICP } > 20 / \# \text{ total hours ICP monitoring}] \times 100$) and the cerebral hypoperfusion index ($[\# \text{ hours of CPP } < 50 / \text{total } \# \text{ hours CPP monitoring} \times 100]$ for ≤ 2 y; $[\# \text{ hours of CPP } < 60 / \text{total } \# \text{ hours CPP monitoring} \times 100]$ for > 2 y) were calculated.

The number of episodes above/below defined thresholds in children with each outcome was compared using C-statistics, as well as 5 day averages. A logistic regression model was used to assess the association and the C-statistic, a measure of the goodness-of-fit of the model used to assess the ability of the number of hours above/below each threshold to discriminate

the outcome. The C-statistics ranges from 0 to 1. A value of 1 would indicate perfect discrimination by the model while a value of 0.5 would indicate discrimination equal to random chance (similar to using the flip of a coin to predict the outcome). Bivariate logistic regression models were used to estimate the association between the intracranial hypertension index and the cerebral hypoperfusion index. A stepwise logistic regression model was used to identify which factors were independently associated with a poor outcome. ICP and CPP are reported in millimeters of mercury.

Results

There were a total of 85 children included in this analysis, including 18 with AHT. Patient demographics are presented in Table 1. There were 6 children who had an initial GCS score > 8 who subsequently deteriorated to GCS ≤ 8 , thereby meeting the definition of severe TBI. There were a total of 34 (40%) children with unfavorable outcome. The mean age of children with unfavorable outcome was younger than those with favorable outcome ($5.2 \text{ y} \pm 0.8$ vs. $6.9 \text{ y} \pm 0.7$), there were 9 deaths (11% mortality rate) of which 2 occurred during the monitoring period of this study. Within the unfavorable outcome cohort, the most common mechanism of injury was AHT (35%, see Table 2). Unfavorable outcome was observed in 66.7% of victims of AHT and 32.8% of victims of accidental TBI (Table 2).

We examined three thresholds of ICP (>14 , >20 and >30), which were used to define intracranial hypertension. For each threshold the number of hours above the threshold for each person was calculated over the first five days after ICP monitor placement. Analyses were then conducted for each threshold to determine if the number of hours above the threshold was associated with outcome. The evaluation of ICP threshold results are shown in Table 3. The model with the number of hours that the ICP exceeded 20 had the best fit ($C=0.641$, 95% confidence interval: 0.523, 0.762). The confidence intervals of the three estimates overlap indicating that there is not a significant difference between the three estimates of fit and no one threshold is superior (or inferior).

A similar approach was used to investigate thresholds for the hours below a specific CPP. Thresholds of CPP (<40 , <45 , <50 , <55 , and <60) were examined. The comparison of the ability of various CPP thresholds to discriminate outcome is shown in Table 3. The model of the number of hours with a CPP < 45 mm Hg provided the best ability to discriminate outcome ($C=0.702$, 95% confidence interval: 0.586, 0.805). As was the case for the ICP thresholds, the confidence intervals of the five estimates overlap indicating that there is not a significant difference between the five estimates of fit and no one threshold is superior (or inferior).

Next we hypothesized that there would be differences in the association of ICP and CPP thresholds with outcomes between children with accidental and abusive TBI mechanisms. The models with the best fit at discriminating outcome using the number of hours above an ICP threshold and the number of hours below a CPP threshold were selected to be used to determine if the mechanism of injury (abuse or not) had a differential impact on the ability of that threshold to discriminate. For ICP, a logistic regression model was fit with main effects for the hours above the threshold, mechanism of injury (abuse, non-abuse) and the

two-way interaction. A statistically significant interaction would indicate a different association in threshold between those abused and not abused. The process was repeated for CPP. As is seen in Table 4, there is no statistically significant interaction between abuse and the threshold for either ICP or CPP, indicating that the threshold does not differ by mechanism.

Both the intracranial hypertension index and the cerebral hypoperfusion index are significantly associated with the outcome, as shown in Table 5. In general, the odds ratio indicates that as each index increases by one unit, the odds of a poor outcome increase (by 5% for the intracranial hypertension index and 3.5% for the cerebral hypoperfusion index).

Only two factors were independently associated with a poor outcome, as seen in Table 6. As the number of hours of ICP > 20 mm Hg increase by 1, the odds of a poor outcome increased by 4.6% (OR=1.046, 95% CI: 1.012, 1.082). Children with AHT had much greater odds of a poor outcome than non-abused children (OR=5.101, 95% CI: 1.571, 16.563).

Discussion

Our study has several findings that could aid clinicians caring for TBI patients and inform the pediatric TBI guidelines. In contrast to assessment of metrics such as number of ICP readings >20 mm Hg, or mean ICP, among others (12, 14–16) we focused our efforts on examination of metrics of ICP burden in children with severe TBI (all mechanisms of injury). While the three ICP thresholds performed similarly in discriminating outcome, we found that the number of hours that ICP is >20 mm Hg was the best fit. Using the same approach, we again found that the CPP thresholds performed similarly with a CPP threshold of <45 mm Hg providing the best ability to distinguish a poor outcome. Surprisingly, there was no difference between victims of accidental vs. AHT in the ability of ICP/ CPP thresholds to discriminate poor outcome. Further confirming that ICP/ CPP burden are important metrics, both the intracranial hypertension index and cerebral hypoperfusion index were significantly associated with outcome. Finally, we found that the number of hours a patient spends with ICP >20 mm Hg, as well as AHT as an injury mechanism, were independently associated with a poor outcome in pediatric severe TBI.

The quantification of ICP/ CPP targets is difficult and we do not fully understand the burden of breaching their critical levels on outcome. Our analysis is similar to prior work, with the strongest association of ICP > 20 mm Hg with poor outcome when including all mechanisms of injury, (6, 12, 14, 16). Indeed, we also found that the threshold of >14 mm Hg performs similarly, which begs the question- should we consider a lower ICP therapeutic target in children? This has certainly been theorized over the years that children may require a lower ICP threshold given their normal lower MAP but has never been shown in prior studies, and a much larger sample from a multicenter initiative would be needed to appropriately test that hypothesis. Chambers and colleagues showed significant differences in mean ICP using the same dichotomized outcome groups as our study, as well as age differences in the mean value of ICP correlating with outcomes, all of which were > 20 mm Hg (15). Adelson et al also found mean ICP was significantly greater in those with poor outcome vs. good outcome (12). However, there is inherent validity in the concept that the

duration of intracranial pressure derangement could be more clinically relevant than any arithmetic mean – which was borne out in our data.

Mean values of variables can be greatly influenced by a few high values and it has been shown by others that episodic ICP increases do not predict outcome. For example, Grinkeviciute et al showed no statistical difference in peak ICP when looking at 6 month outcomes in pediatric TBI (16). A study reported in adults examined ICP in terms of “dose” (defined by area under the curve of ICP > 20 mm Hg over time) of intracranial hypertension. This dose was associated with poor outcomes at 6 months (17). This method also speaks to the need to further characterize increased ICP as more of a burden of disease rather than isolated episodes of an abnormality. We also found that the intracranial hypertension index was significantly associated with outcome, speaking to the relative importance of ICP burden over episodic measurements. However, characterizing the burden of ICP and use of the intracranial hypertension index is difficult to calculate at the bedside and may not be the most useful tool for either acute prognostication or titration of therapies. It may be more helpful in long term prognostication once the acute critical care period is over.

We also found that the duration of derangement of CPP appears to be more significant than overall mean values. Similar to the study by Downard et al, we found that the CPP parameter that best discriminated poor outcome was number of hours spent with CPP < 45 mm Hg (14). Our data examining CPP burden appear to confirm and build on that report. Our data did not identify a continuum but did indicate that although 45 mm Hg performed best, a number of other thresholds performed similarly. Another study in children showed that 70% of their population with an initial CPP < 40 mm Hg had unfavorable outcome (18). Allen et al recently found age related CPP thresholds associated with poor outcome, showing that time spent below specific thresholds was related to decreased survival (19). Adelson et al found that the percent of time with CPP > 50 mm Hg was greater in children with good vs. poor outcome (12). The cerebral hypoperfusion index was significantly associated with outcome. Indeed for both ICP and CPP a personalized threshold may ultimately need to be derived based not only on ICP and CPP values, but additional information such as brain tissue oxygenation, microdialysis monitoring, or pressure reactivity index, as was suggested recently in the work of Weersink et al and Allen et al (19, 20).

In addition to exploring the impact of burden of ICP and CPP, another goal was to address the lack of data on infants with severe TBI resulting from AHT in the guidelines; and as to whether or not AHT is a different disease than accidental TBI. Surprisingly, we found no significant differences in the associations between ICP and CPP and outcome in the AHT vs. accidental cohorts. This may in part reflect a somewhat smaller sample size of this population in our study (18 patients). However, in support of our findings, a recent paper analyzing a subset of our cohort of < 2y TBI subjects found a similar lack of association between ICP thresholds and outcome in infants with AHT and only a single CPP threshold, namely, CPP <45 mm Hg to be associated with unfavorable outcome (21). There may be several explanations for these observations. AHT victims may have limited autoregulatory reserve (22). This may make younger children more vulnerable to secondary injury with decreased MAP and CPP. There also appears to be frequent loss of blood pressure autoregulation of cerebral blood flow (CBF) in this group. In a unique, albeit exploratory

study, Vavilala et al. (23) showed that all 3 of the AHT patients in their cohort had impaired autoregulation in at least one hemisphere. All 3 had poor outcome vs. accidental TBI in which no patient with unilateral loss of autoregulation had poor outcome. Finally, the role of an open fontanel in infants with TBI and its impact on intracranial dynamics and/or CBF remains unclear.

Given the remarkably poor outcome in AHT, yet lack of a different threshold between accidental and AHT, one could interpret our findings as evidence that improving outcome will require treatment directed at alternate targets. Consistent with that possibility, Mehta et al found that 9/11 children with unfavorable outcome after severe TBI exhibited little of the ICP burden in their study of whom ~ 80% were AHT and all were < 2y (21). This supports the thought that ICP may be a particularly insensitive marker of the overall damage in AHT. In contrast to that supposition, Cho et al. (24) found decreased mortality and improved outcomes after decompressive craniectomy in children <2y with AHT. There was a significant decrease in ICP after decompressive craniectomy in these patients, suggesting that ICP is important in AHT. In our institution, unlike many others, ICP is routinely monitored in AHT patients and intracranial hypertension and cerebral hypoperfusion are aggressively treated in the same manner as accidental TBI. We found that ICP and CPP performed similarly in discriminating outcome in all mechanisms of injury, arguing against those that have suggested there is no role for ICP monitoring in AHT. In any case, these differences in data and the high rate of unfavorable outcomes may still suggest that AHT represents a different disease than accidental TBI and that future studies should address all aspects of TBI care in that specific population. Thus, there is a formidable and important gap in the literature as many studies either exclude AHT or children <1–2 years of age who are more likely to be victims of abuse (15, 18, 25). Our sample size, although representing one of the largest cohorts of ICP monitoring in AHT to be reported in, is still limited.

There are several limitations to our study. First, the practice of targeting specific threshold values of ICP (20 mm Hg) and CPP (50 or 60 mm Hg) during our routine care confounds our findings and may bias the specific thresholds associated with outcome. Second, while the data were prospectively collected, they were retrospectively reviewed. Since informed consent was required for enrollment in our database, not all subjects with severe TBI were capable of being studied. Third, we reported significant associations between deranged ICP/CPP and unfavorable outcome; however we did not provide conclusive evidence that altering these deranged values with therapies would improve outcome. There are likely age-related ICP/CPP thresholds, however our sample size would unlikely determine statistically relevant differences in our population. Specific prospective studies are needed to define the values that should prompt treatment and the influence these treatments may have on outcome. Finally, the use of the GOS score in children and especially infants may not represent the optimal approach to defining outcome. While the GOS score is a gold standard in TBI outcome, it does not provide a very meaningful assessment of an infant/child's outcome especially in regards to ongoing neurodevelopment. We anticipate the ongoing ADAPT trial will provide more meaningful outcome measures given the extensive neuropsychological testing required.

Conclusions

We found that the duration of hours of ICP >20 mm Hg and CPP < 45 mm Hg were the best fit for associations with poor outcome in pediatric severe TBI, and that these thresholds were consistent across both accidental and AHT. Larger studies need to be undertaken to confirm if these are the optimal therapeutic targets. We report that an increased intracranial hypertension index as well as an increased cerebral hypoperfusion index are also associated with poor outcome in pediatric TBI, and given the finding that for each hour ICP is > 20 mm Hg there was a 4.6% increase in poor outcome, our findings further support the concept of the importance of ICP/ CPP burden.

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Table 1

Demographic Data

	Unfavorable (n=34)	Favorable (n=51)
Age, years	5.1 ± 0.8	6.5 ± 0.6
GCS (median)	6	7
Gender	18 male (53%)	35 male (69%)
Outcome	GOS 3 = 24 (71%)	GOS 1 = 34 (67%)
	GOS 4 = 1 (3%)	GOS 2 = 17 (33%)
	GOS 5 = 9 (26%)	

Table 2

Mechanism of Injury

Mechanism of injury	Unfavorable n = 34	Favorable n = 51
Abuse	12 (35%)	6 (12%)
Car vs. Ped	1 (3%)	11 (22%)
Fall	7 (20%)	17 (32%)
MVA	7 (20%)	11 (22%)
Recreational	2 (7%)	5 (10%)
Other	5 (15%)	1 (2%)

Table 3
ICP and CPP Thresholds For All Mechanisms of Injury

Fit of Model for Different ICP and CPP thresholds for Predicting a Poor Outcome (GOS of 3 or higher)

		95% Confidence Interval	
ICP Threshold	C-statistic	Lower-bound	Upper-bound
Hours > 14	0.620	0.511	0.748
Hours > 20	0.641	0.523	0.762
Hours > 30	0.600	0.491	0.716
CPP Threshold			
Hours < 40	0.657	0.560	0.765
Hours < 45	0.702	0.586	0.805
Hours < 50	0.684	0.559	0.795
Hours < 55	0.643	0.509	0.764
Hours < 60	0.662	0.540	0.789

Table 4

Differential Effect of ICP or CPP threshold by Abuse Status

Threshold Model	Abuse		ICP or CPP Threshold		Interaction	
	Parameter Estimate	p-value	Parameter Estimate	p-value	Parameter Estimate	p-value
Hours ICP > 20	1.752	0.0099	0.048	0.0121	-0.017	0.6838
Hours CPP < 45	1.155	0.092	0.164	0.105	--0.081	0.5431

Table 5

Association of Intracranial Hypertension Index and Cerebral Hypoperfusion Index on a Poor Outcome

	Odds Ratio	p-value	C-statistic
Intracranial Hypertension Index	1.050	0.012	0.656
Cerebral Hypoperfusion Index	1.035	0.017	0.609

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Table 6

Factors Independently Associate with a Poor Outcome

	Odds Ratio	p-value
Abuse	5.101	.0067
Hours ICP > 20	1.046	0.086

* Factors examine which were not retained in the model are: cerebral hypoperfusion index, intracranial hypertension index, hours CPP < 45, age, sex, GCS.