Brain Hypoxia Is Associated With Short-term Outcome After Severe Traumatic Brain Injury Independently of Intracranial Hypertension and Low Cerebral Perfusion Pressure

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BACKGROUND: Brain hypoxia (BH) can aggravate outcome after severe traumatic brain injury (TBI). Whether BH or reduced brain oxygen ($Pbto_2$) is an independent outcome predictor or a marker of disease severity is not fully elucidated.

OBJECTIVE: To analyze the relationship between $Pbto_2$, intracranial pressure (ICP), and cerebral perfusion pressure (CPP) and to examine whether BH correlates with worse outcome independently of ICP and CPP.

METHODS: We studied 103 patients monitored with ICP and $Pbto_2$ for $>$ 24 hours. Durations of BH ($Pbto_2 < 15$ mm Hg), ICP $>$ 20 mm Hg, and CPP $<$ 60 mm Hg were calculated with linear interpolation, and their associations with outcome within 30 days were analyzed.

RESULTS: Duration of BH was longer in patients with unfavorable (Glasgow Outcome Scale score, 1-3) than in those with favorable (Glasgow Outcome Scale, 4-5) outcome (8.3 $\pm$ 15.9 vs 1.7 $\pm$ 3.7 hours; $P < .01$). In patients with intracranial hypertension, those with BH had fewer favorable outcomes (46%) than those without (81%; $P < .01$); similarly, patients with low CPP and BH were less likely to have favorable outcome than those with low CPP but normal $Pbto_2$ (39% vs 83%; $P < .01$). After ICP, CPP, age, Glasgow Coma Scale score, Marshall computed tomography grade, and Acute Physiology and Chronic Health Evaluation II score were controlled for, BH was independently associated with poor prognosis (adjusted odds ratio for favorable outcome, 0.89 per hour of BH; 95% confidence interval, 0.79-0.99; $P = .04$).

CONCLUSION: Brain hypoxia is associated with poor short-term outcome after severe traumatic brain injury independently of elevated ICP, low CPP, and injury severity. $Pbto_2$ may be an important therapeutic target after severe traumatic brain injury.

KEY WORDS: Brain hypoxia, Brain tissue oxygen pressure, Cerebral perfusion pressure, Indepedent predictor, Intracranial Pressure, Outcome, Traumatic brain injury

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Traumatic brain injury (TBI) remains a leading cause of death and disability among young people worldwide. Poor outcome is associated with delayed secondary cerebral damage that develops hours to days after the initial insult. Brain hypoxia is a common cause of secondary cerebral damage after severe TBI.[1] Efforts to maintain adequate interstitial partial pressure of oxygen in brain tissue ($Pbto_2$) therefore may play an important role in the management of severe TBI patients. $Pbto_2$ may be monitored continuously at the bedside; the use of $Pbto_2$ monitors was recently incorporated into the guidelines for severe traumatic brain injury[2] on the basis of the notion that brain hypoxia, defined by a $Pbto_2 < 15$ mm Hg, may be diagnosed and corrected before irreversible damage occurs.[3]

ABBREVIATIONS: AOR, adjusted odds ratio; **APACHE II,** Acute Physiology and Chronic Health Evaluation II; **CI,** confidence interval; **CPP,** cerebral perfusion pressure; **GCS,** Glasgow Coma Scale; **ICP,** intracranial pressure; **IQR,** interquartile range; **MAP,** mean arterial pressure; **TBI,** traumatic brain injury

Previous clinical observations demonstrate an association between brain hypoxia and outcome after severe TBI.[4-6] Overall, these studies include few patients but suggest that brain hypoxia may be an independent factor associated with poor outcome. Work by van den Brink et al[4] suggests that the effect of brain hypoxia is independent of intracranial hypertension. However, it remains to be fully elucidated whether brain hypoxia is simply a marker of injury severity and its effects depend on intracranial pressure (ICP) and cerebral perfusion pressure (CPP) or whether the association between $Pbto_2$ and outcome is independent of the morphological and physiological effects of TBI, including those from increased ICP or reduced CPP.[7,8]

In this study, we examined 103 patients who had both continuous $Pbto_2$ and ICP monitoring for at least 24 hours after severe nonpenetrating TBI. We hypothesized that brain hypoxia is associated with worse short-term outcome after severe TBI and that this association is independent of intracranial hypertension, low CPP, and the morphological or physiological consequences of the TBI. In addition, we used a linear interpolation method to examine the origin of secondary brain hypoxic insults and the relationship among reduced $Pbto_2$, elevated ICP, and low CPP.

METHODS

Patients

Subjects included in this study were identified retrospectively from a prospective observational database (Brain Oxygen Monitoring Outcome study) that describes patients with severe TBI treated in the neurointensive care unit at the Hospital of the University of Pennsylvania, Philadelphia, an academic level 1 trauma center. Approval for the study was obtained from the Institutional Review Board. Traumatic brain injury was defined by a history of trauma and clinical and radiographic exclusion of alternative causes of coma. Patients included in this study had nonpenetrating TBI and both $Pbto_2$ and ICP monitoring if at any time during hospitalization their Glasgow Coma Scale (GCS) score was ≤ 8. Patients were excluded who had fixed and dilated pupils at admission, had $<$ 24 hours of intracranial monitoring, had $Pbto_2$ = 0 mm Hg for $>$ 3 hours, or were declared brain dead within 48 hours of initiation of monitoring.

Intracranial Monitoring

Intracranial pressure, brain temperature, and $Pbto_2$ were monitored continuously with a Licox monitor (Integra Neuroscience, Plainsboro, New Jersey) as part of standard patient care when their GCS was ≤ 8.[9] All 3 intracranial monitors were inserted at the bedside through the same burr hole into the frontal lobe and secured with a triple-lumen bolt. The $Pbto_2$ monitor was placed into white matter that appeared normal on the admission head computed tomography (CT) and on the side of maximal pathology. When there was no asymmetry in brain pathology on CT, the probes were placed in the right frontal region. If the patient had undergone a craniotomy, the probes were placed on the same side as the injury if the craniotomy flap permitted. Follow-up noncontrast head CT scans were performed in all patients within 24 hours of admission to confirm correct placement of the various monitors, eg, not in a contusion or infarct. Probe function and stability were confirmed by an oxygen challenge (Fio_2, 1.0 for 2 minutes). To allow for probe equilibration, data from the first 3 hours after ICP and $Pbto_2$ monitor insertion were discarded. Each patient also had an indwelling arterial (usually radial artery) catheter, and mean arterial pressure (MAP) was recorded continuously in all patients. Cerebral perfusion pressure was calculated from the measured parameters (CPP = MAP $-$ ICP). Heart rate and arterial oxygen saturation (Sao_2) also were recorded in all patients. Intracranial monitors were removed when ICP was normal for 24 hours without treatment or when the patient was able to follow commands.

General Clinical Management

All patients were resuscitated and managed according to a protocol based on published recommendations for severe TBI and intensive care unit (ICU) care.[10] This included (1) early identification and evacuation of traumatic hematomas; (2) intubation and ventilation with low-volume pressure-limited ventilation to maintain $Paco_2$ between 30 and 40 mm Hg and Sao $>$ 93%; (3) sedation with propofol during the first 24 hours, followed by sedation and analgesia with lorazepam, morphine, or fentanyl; (4) bed rest with head elevation initially of $\geq 30°$; (5) normothermia of approximately 35°C to 37°C; (6) euvolemia using a baseline crystalloid infusion (0.9% normal saline, 20 mEq/L KCl; 80-100 mL/h); (7) anticonvulsant prophylaxis with phenytoin for $\geq$ 1 week if seizures occurred; and (8) packed red blood cell transfusion if their hemoglobin was $<$ 7 mg/dL. Goals of therapy included maintaining ICP $<$ 20 mm Hg and CPP $>$ 60 mm Hg.

Management of Intracranial Hypertension

Elevated ICP ($>$ 20 mm Hg for $>$ 2 minutes) was initially treated with elevation of the head of the bed, sedation (lorazepam), and analgesia (fentanyl). If ICP remained $>$ 20 mm Hg for $>$10 minutes despite these initial measures, osmotherapy was administered using repeated boluses of mannitol (1 g/kg, 25% solution), provided that the serum osmolar gap was $<$ 20. Thereafter, cerebrospinal fluid was drained with an external ventricular drain, particularly if there was hydrocephalus. Second-tier therapies for refractory intracranial hypertension ($>$ 20 mm Hg for $>$ 15 minutes in a 1-hour period despite therapy) included optimized hyperventilation ($Paco_2$, 30-35 mm Hg), decompressive craniectomy, or pharmacological coma (with propofol or pentobarbital). Induced hypothermia and hypertonic saline for ICP control were not used to manage ICP in the patients included in this study. Therapeutic intensity level was calculated as previously described,[11] and for each patient, we analyzed the correlation between the maximum therapeutic intensity level and both the duration of brain hypoxia and elevated ICP.

Management of Brain Oxygen

Patients received "cause"-directed therapy to maintain $Pbto_2 \geq 20$ mm Hg according to our local protocol.[9,12] When $Pbto_2$ was low in the setting of intracranial hypertension (ICP $>$ 20 mm Hg), measures were taken to lower ICP as described above. If ICP $<$ 20 mm Hg or lowering ICP failed to raise $Pbto_2$, then CPP was increased (usually with phenylephrine). If the cause of low $Pbto_2$ was systemic hypoxia, then pulmonary function was optimized with the mechanical ventilator (eg, by increasing Fio_2 and/or positive end-expiratory pressure). If excess metabolic demand was suspected (eg, owing to pain, agitation, fever, or seizures), then analgesic, sedative, or antiepileptic medications were administered. If these measures failed and hemoglobin was $<$ 10 mg/dL, then a blood transfusion was administered. A decompressive craniectomy was considered if there was a progressive $Pbto_2$ decline or $Pbto_2$ was $\leq$ 20 mm Hg for $>$ 15 minutes despite maximal medical management for elevated ICP.

Data Collection and Analysis

Clinical and radiological variables included age, admission (post-resuscitation) GCS, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Marshall CT scan classification.[13,14] Marshall CT classification was determined by consensus of a neurointensivist, a neuroradiologist, and a non-ICU neurologist who examined admission head CT scans in random order and who were blinded to patient outcome. Presence/absence of traumatic subarachnoid hemorrhage and intraventricular hemorrhage was also assessed on the CT scan. Clinical information was obtained from patient hospital records. Detailed information on prehospital care was unavailable.

Physiological variables, including $Pbto_2$, ICP, MAP, and CPP, were monitored continuously at the bedside (Component Monitoring System M1046-9090C, Hewlett Packard, Andover, Massachusetts) and were recorded in the ICU flow sheet usually every 15 minutes and at least every 30 minutes. Thresholds of physiological abnormality were defined as follows: $Pbto_2 < 15$ mm Hg,[2] ICP > 20 mm Hg[15], and CPP < 60 mm Hg.[16] These thresholds were chosen to be consistent with current recommendations in the guidelines for the management of severe traumatic brain injury. Brain hypoxia was defined as a $Pbto_2 < 15$ mm Hg of > 30 minutes in duration.[2] Because of the large and variable number of repeated physiological measurements and abnormal episodes over the duration of monitoring, for each individual patient, single episodes of physiological abnormality were identified and their duration was determined with linear interpolation[17] (Figure 1). This method allowed us to measure the total duration (sum of the duration of single episodes) of low $Pbto_2 < 15$ mm Hg, elevated ICP > 20 mm Hg, and low CPP < 60 mm Hg. The relationship between $Pbto_2$ and CPP was further analyzed within each individual patient by calculating the total time during which episodes of brain hypoxia and CPP < 60 mm Hg occurred simultaneously and the percentage of brain hypoxic time with normal CPP ≥ 60 mm Hg.

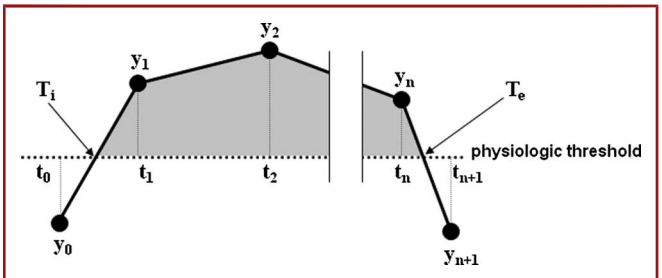

FIGURE 1. *Definitions and calculations related to a single episode of physiological abnormality. The y with indexes designates successive recorded values of the physiological variable, whether brain tissue oxygen tension ($Pbto_2$), intracranial pressure (ICP), or cerebral perfusion pressure (CPP). Each y falls either on the physiological side or on the abnormal side of a threshold value (ie, ICP > 20 mm Hg, CPP < 60 mm Hg, $Pbto_2 < 15$ mm Hg; dotted line). A single episode is a sequence of successive values, each beyond threshold. The figure illustrates an example of abnormal physiological episode, with the last normal value before the episode (y_0), the first (y_1) and last (y_n) value falling within the episode, and the first normal value after the episode (y_{n+1}), with t_0, t_1, t_n, and t_{n+1} being the corresponding times. The episode time boundaries T_i and T_e are determined by linear interpolation as shown. If the time interval separating y_1 from y_0 ($t_1 - t_0$) exceeded 2 hours, T_i was set equal to t_1. The same rule applies to the determination of T_e. Duration of the abnormal physiological value equals the time between T_i and T_e.*

Cause of Secondary Brain Hypoxic Insults

For each patient, we determined the cause of every brain hypoxic episode. The cause of brain hypoxia was classified as follows: (1) CPP decrease of at least 10 mm Hg, resulting from either ICP increases > 20 mm Hg (low CPP/high ICP) or MAP decreases of at least 10 mm Hg (low CPP/low MAP); (2) $Pao_2 < 90$ mm Hg; (3) hemoglobin concentration < 9 g/dL; (4) hyperthermia > 38.3°C or induced cooling; and (5) unknown/unidentifiable, in cases when we were unable to find the exact cause of brain hypoxia.

Outcome Assessment

A neurointensivist and a neurocritical nurse independently assessed short-term outcome within 30 days of injury. Outcome was assessed with the Glasgow Outcome Scale score dichotomized as favorable (Glasgow Outcome Scale score of 4 = moderate disability or 5 = good recovery) or unfavorable (Glasgow Outcome Scale score of 1 = death, 2 = vegetative state, and 3 = severe disability requiring long-term rehabilitation facility or skilled nursing facility).

Statistical Analysis

Statistical analysis was performed with the Stata 9 software package (StataCorp LP, College Station, Texas). A value of $P < .05$ was considered statistically significant. To examine associations between clinical, radiological, and physiological variables and outcome, univariate comparisons were performed with the Student t or Mann-Whitney U test (for continuous variables and according to the distribution of the data) or the χ^2 test (for categorical variables). The following variables were analyzed: age, admission GCS, Marshall CT classification, APACHE II score (without GCS inclusion), duration of brain hypoxia, elevated ICP, and low CPP. All variables with a significance level $< .2$ on univariate analysis were candidates for inclusion in a multivariable logistic regression model in which the dependent variable was the neurological outcome dichotomized as favorable or unfavorable. A stepwise forward approach was used for variable selection, with P values to include of .15 and P values to exclude of .2; therefore, only variables with a value of $P < .2$ were retained by the final model. Likelihood ratio test was used to compare the fit of the models.

RESULTS

Study Population

One hundred three patients (mean age, 43 ± 19 years) with severe TBI who were hospitalized between October 2002 and October 2005 were included in this study. Another 31 patients managed during the same time period were excluded from analysis because of penetrating TBI (n = 10), ICP and $Pbto_2$ monitoring that lasted < 24 hours (n = 8), $Pbto_2 = 0$ mm Hg with a confirmed diagnosis of brain death within 48 hours of the start of intracranial monitoring (n = 8), and incomplete data (n = 5). Individual patient clinical and radiological characteristics are summarized in Table 1. The majority of patients (79%) had traumatic subarachnoid hemorrhage or intraventricular hemorrhage on admission CT scan.

Prevalence of Brain Hypoxia, Elevated ICP, and Low CPP During Intracranial Monitoring

Data on $Pbto_2$ and ICP monitoring are summarized in Table 2. The median time from admission to intracranial monitoring was

TABLE 1. Baseline Patient Characteristics[a]

Characteristic	Study Population (n = 103)
Age, y	43 ± 19
Female sex, n (%)	23 (29)
Admission GCS,[b] n (%)	
3-4	52 (50)
5-6	15 (14)
7-8	16 (16)
> 8	20 (20)
Marshall head CT classification, n (%)	
2	21 (20)
3	31 (30)
4	8 (8)
5	43 (42)
APACHE II score, n (%)	
< 16	21 (20)
16-20	36 (35)
20-25	31 (30)
> 25	15 (15)

[a]APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Scale. Data are expressed as mean ± SD when appropriate.
[b]The GCS listed is the postresuscitation GCS in the emergency room. Twenty patients had an initial GCS > 8 but subsequently deteriorated and required intracranial monitoring (ie, GCS ≤ 8).

6 hours (interquartile range [IQR], 3-13 hours). Median maximal therapeutic intensity level during intracranial monitoring was 8 (range, 5-18).

Etiology of Brain Hypoxic Insults

Figure 2 illustrates the suspected cause of brain hypoxia. A CPP decrease, because either ICP increased (low CPP/high ICP, 50%) or MAP decreased (low CPP/low MAP, 25%), was frequently associated with brain hypoxia. Our CPP threshold for treatment was 60 mm Hg: CPP was ≥ 60 mm Hg over a median of 48% (IQR, 3%-93%) of brain hypoxic time. The wide interindividual range suggests that individual CPP thresholds for brain hypoxia vary between patients and may often be > 60 mm Hg. Other factors associated with brain hypoxia were hyperthermia (5%), induced cooling (7%), Pao_2 < 90 mm Hg (8%), and hemoglobin concentration < 9 g/dL (2%).

TABLE 2. Prevalence of Brain Hypoxia ($Pbto_2$ < 15 mm Hg), Intracranial Hypertension (Intracranial Pressure > 20 mm Hg), and Low Cerebral Perfusion Pressure (< 60 mm Hg) Over the Entire Duration of Intracranial Monitoring[a]

Variable	
Duration of intracranial monitoring, d	5 ± 3
Patients with brain hypoxia, n (%)	55 (54)
Mean patient duration of brain hypoxia, h	8.6 ± 14.4
Patients with intracranial hypertension, n (%)	74 (73)
Mean patient duration of intracranial hypertension, h	24.8 ± 31.2
Patients with low CPP, n (%)	75 (74)
Mean patient duration of low CPP, h	10.2 ± 12.3

[a]CPP, cerebral perfusion pressure. Data are expressed as mean ± SD when appropriate.

The Relationship Between $Pbto_2$, ICP, and CPP

The relationship between $Pbto_2$, ICP, and CPP was analyzed within the entire patient cohort (Table 3). Patients with elevated ICP and low CPP were more likely to have brain hypoxia (43 of 74 [58%] and 46 of 75 [61%], respectively), whereas $Pbto_2$ was always ≥ 15 mm Hg in many patients with normal ICP (16 of 28 [57%]) and normal CPP (18 of 28 [63%]). However, brain hypoxia also was observed in patients with normal ICP (12 of 28 [43%]) and in those with normal CPP (9 of 27 [33%]), whereas 31 of 74 patients (42%) with elevated ICP and 29 of 75 patients (39%) with low CPP had no episodes of $Pbto_2$ < 15 mm Hg. Therapeutic intensity level correlated with the duration of elevated ICP (Pearson r linear correlation coefficient, 0.53; $P < .001$) but not with the duration of brain hypoxia ($r = 0.14$, $P = .29$).

Factors Associated With Outcome

Favorable outcome (good recovery, n = 37, or moderate disability, n = 21) was observed in 58 patients (57%). Thirty-seven patients had died and 8 were vegetative or severely disabled at 30 days. The duration of monitoring was not associated with outcome (85 hours [IQR, 45-165 hours] in patients with favorable vs 77 hours [IQR, 46-113 hours] in those with unfavorable outcome; $P = .17$, Mann-Whitney U test). Time to monitoring was also comparable between the 2 outcome groups (6 hours [IQR, 3-16 hours] vs 7 hours [IQR, 4-11 hours]; $P = .93$, Mann-Whitney U test).

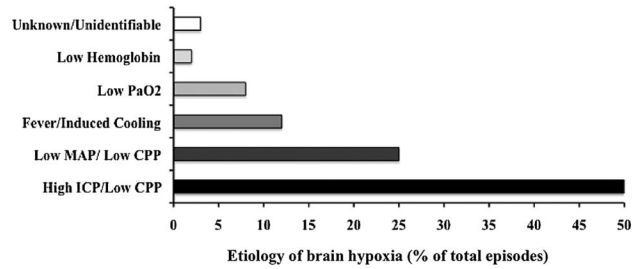

FIGURE 2. *Cause of brain hypoxic insults. Histograms illustrate the potential causes of brain hypoxia classified as follows: (1) cerebral perfusion pressure (CPP) decrease of at least 10 mm Hg, either because intracranial pressure (ICP) increased > 20 mm Hg (low CPP/high ICP) or because mean arterial pressure (MAP) decreased at least 10 mm Hg (low CPP/low MAP); (2) Pao_2 < 90 mm Hg; (3) hemoglobin concentration < 9 g/dL; (4) hyperthermia > 38.3°C or induced cooling; or (5) unknown/unidentifiable, ie, unable to find the exact cause of brain hypoxia.*

TABLE 3. Number of Patients With High vs Normal Intracranial Pressure and With Low vs Normal Cerebral Perfusion Pressure Expressed as a Function of $Pbto_2$ Values[a]

	Patients With ICP > 20 mm Hg	Patients With ICP 0 – 20 mm Hg
Patients with $Pbto_2$ < 15 mm Hg (n = 55)	43	12
Patients with $Pbto_2$ ≥ 15 mm Hg (n = 47)	31	16
Total (n = 102)	74	28

	Patients With CPP < 60 mm Hg	Patients With CPP ≥ 60 mm Hg
Patients with $Pbto_2$ < 15 mm Hg (n = 55)	46	9
Patients with $Pbto_2$ ≥ 15 mm Hg (n = 47)	29	18
Total (n = 102)	75	27

[a]CPP, cerebral perfusion pressure; ICP, intracranial pressure. Data on ICP and CPP were incomplete in 1 patient.

Table 4 lists univariate associations between outcome and all clinical, radiological, and physiological variables. Age, admission GCS, Marshall CT classification, APACHE II score, duration of brain hypoxia, and high ICP were significantly associated with outcome. Alone, the duration of low CPP was not associated with outcome. However, Table 4 also shows that time when CPP < 60 mm Hg occurred simultaneously with $Pbto_2$ < 15 mm Hg was longer in patients with an unfavorable than in those with a favorable outcome, thereby suggesting that low CPP has significant prognostic value, particularly when it is associated with brain hypoxia. A similar association between the duration of brain hypoxia and outcome was found when only the first 24 hours of intracranial monitoring were examined (0.7 ± 1.8 hours in patients with favorable vs 4.2 ± 8.8 hours in those with unfavorable outcome; $P < .001$).

Brain Hypoxia and Outcome

We further examined the impact of brain hypoxia on outcome in the subgroup of patients with intracranial hypertension and low CPP (Table 5). When there was intracranial hypertension, the presence of brain hypoxia was associated with fewer favorable outcomes (46% vs 81% in patients with high ICP but normal $Pbto_2$; $P < .01$). Similarly, in patients who had both low CPP and brain hypoxia, 39% had a favorable outcome vs 83% of those with low CPP but normal $Pbto_2$ ($P < .01$).

Brain Hypoxia Is Associated With Outcome After Severe TBI

All variables with a significance level < .2 on univariate analysis (Table 4) were included in a multivariable logistic regression model. A stepwise forward approach was used for variable selection with *P* values to include of .15 and *P* values to exclude of .2. Likelihood ratio test was used to compare the fit of the models. Only variables with a value of $P < .2$ were retained in the final multivariable model (Table 6). With this model, brain hypoxia was an independent predictor of poor prognosis in our cohort of severe TBI, with an adjusted odds ratio (AOR) for favorable outcome of 0.89 (95% confidence interval [CI], 0.79-0.99) per hour spent with a $Pbto_2$ < 15 mm Hg ($P = .04$). Other factors associated with outcome in multivariable analysis included Marshall CT classification (AOR, 0.42; 95% CI, 0.25-0.71; $P = .01$), admission GCS (AOR, 1.21; 95% CI, 1.02-1.44; $P = .03$), and APACHE II score (AOR, 0.86; 95% CI, 0.73-1.00; $P = .05$). Intracranial hypertension (duration of ICP > 20 mm Hg) was retained as a prognostic predictor by the final model, although it did not reach statistical significance (AOR for favorable outcome, 0.99 per hour of ICP > 20 mm Hg; 95% CI, 0.98-1.01; $P = .11$).

TABLE 4. Factors Associated With Outcome on Univariate Analysis[a]

Variable	Favorable Outcome (GOS, 4-5) (n = 58)	Unfavorable Outcome (GOS, 1-3) (n = 45)	*P*
Age, y	38 (26-51)	47 (28-69)	< .01[b]
Admission GCS	6 (3-9)	3 (3-6)	< .01[b]
Marshall CT classification (admission)	3 (2-4)	5 (3-5)	< .001[b]
APACHE II score	17 (15-21)	22 (19-25)	< .001[b]
$Pbto_2$ < 15 mm Hg duration, h	1.7 ± 3.7	8.3 ± 15.9	< .01[b]
ICP > 20 mm Hg duration, h	11.5 ± 16.5	21.6 ± 29.6	.03[b]
CPP < 60 mm Hg duration, h	6.5 ± 9.7	8.2 ± 8.3	.35
CPP < 60 mm Hg + $PbtO_2$ < 15 mm Hg duration, h	0.8 ± 2.3	3.3 ± 7.4	.02[b]

[a]APACHE II, Acute Physiology and Chronic Health Evaluation II; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; ICP, intracranial pressure. Using a linear interpolation method, we calculated for each patient the total duration of brain hypoxia (defined by a $PbtO_2$ < 15 mm Hg), high ICP (defined by an ICP > 20 mm Hg), and low CPP (defined by a CPP < 60 mm Hg). Total duration of episodes when low CPP and low $PbtO_2$ occurred simultaneously also is provided. Data are expressed as median (interquartile range) or mean ± SD.
[b]Significant.

TABLE 5. Outcome in Patients With Intracranial Hypertension (Intracranial Pressure > 20 mm Hg) and Low Cerebral Perfusion Pressure (< 60 mm Hg) According to the Presence or Absence of Brain Hypoxia ($PbtO_2$ < 15 mm Hg)[a]

	Patients With Favorable Outcome, n (%)	
	Intracranial Hypertension (n = 74)	Low CPP (n = 75)
Brain hypoxia	20/43 (46)	18/46 (39)
No brain hypoxia	25/31 (81)	24/29 (83)
P	< .01	< .01

[a]CPP, cerebral perfusion pressure.

DISCUSSION

In this retrospective analysis of a prospective observational cohort of 103 severe TBI patients who had an ICP and $Pbto_2$ monitor for > 24 hours, we examined whether short-term outcome after severe TBI is associated with brain hypoxia ($Pbto_2$ < 15 mm Hg) independently of high ICP (> 20 mm Hg) and low CPP (< 60 mm Hg). The important finding of this study is that brain hypoxia (low $Pbto_2$ < 15 mm Hg) is associated with poor short-term outcome after severe TBI independently of elevated ICP and low CPP. This finding seems to suggest that $Pbto_2$ may be a better physiological prognostic marker than ICP and CPP in patients with severe TBI. We also observed that although brain hypoxia can be associated with a decrease in CPP, brain hypoxia may occur despite CPP being within normal ranges and greater than the usual therapeutic threshold. In addition, brain hypoxia was associated with unfavorable outcome independently of other known predictors of outcome, including age, admission GCS, Marshall grade, and APACHE II score, thereby suggesting that $Pbto_2$ may be a reasonable therapeutic target in some severe TBI patients. Taken together, our data support the use of $Pbto_2$ monitors after severe TBI and warrant further study to evaluate whether strategies to prevent and treat brain hypoxia may help improve TBI outcome.

TABLE 6. Independent Predictors of Outcome by Multivariable Analysis[a]

Variable	Adjusted OR for Favorable Outcome	95% CI	Adjusted *P*
Marshall CT classification	0.42	0.25-0.71	.01[e]
Admission GCS	1.21	1.02-144	.03[e]
APACHE II score[b]	0.86	0.73-1.00	.05[e]
Brain hypoxia[c]	0.89	0.79-0.99	.04[e]
Intracranial hypertension[d]	0.99	0.98-1.01	.11

[a]APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio. All variables with a significance level < .2 on univariate analysis were included in a multivariable logistic regression model in which the dependent variable was the neurological outcome at 30 days dichotomized as favorable (Glasgow Outcome Scale [GOS], 4 [moderate disability], and 5 [good recovery]) or unfavorable (GOS, 1 [death], 2 [vegetative state], and 3 [severe disability]). A stepwise forward approach was used for variable selection, with *P* values to include of .15 and to exclude of .2. Variables with *P* > .2 (age, low CPP) therefore are not shown in the final model. The adjusted OR for favorable outcome was 0.89 per hour of brain hypoxia.
[b]APACHE II score was calculated without the inclusion of GCS.
[c]Duration of $Pbto_2$ < 15 mm Hg.
[d]Duration of intracranial pressure > 20 mm Hg.
[e]Significant.

The Need for $Pbto_2$ Monitors

In recent years, the use of $Pbto_2$ monitors has increased in the management of TBI patients.[2,3] Data from other clinical studies in which alternative techniques such as cerebral microdialysis, positron emission tomography, and retrograde jugular catheters were used demonstrate that brain hypoxia or cell metabolic dysfunction may occur in the absence of ischemia and when CPP is normal.[18-20] We previously observed that one-third of severe TBI patients who are adequately resuscitated according to established guidelines still have evidence for brain hypoxia in the early hours after TBI.[21] Similarly, a recent retrospective series of 27 TBI patients[22] suggested that elevated ICP and/or low CPP are not the only causes of reduced $Pbto_2$ after severe TBI. Prospective observational studies demonstrate that fewer than half the episodes of brain hypoxia after TBI are associated with low CPP resulting from either increased ICP or decreased MAP[23] and that metabolic changes, eg, lactate elevation, may precede the increase in ICP.[23] In the present study, a CPP decrease was a frequent cause of brain hypoxia, together with low Pao_2, hyperthermia, induced cooling, and low hemoglobin concentration. In many instances, several factors occurred together. However, the CPP was ≥ 60 mm Hg during a median of 48% of brain hypoxic time. The wide interindividual range (3%-93%) suggests that individual CPP thresholds for brain hypoxia varies between patients and in many patients may be > 60 mm Hg. Together, these data suggest that some secondary brain hypoxic insults may go undetected if ICP and CPP are monitored alone. This supports the use of both ICP and $Pbto_2$ monitors to help optimize the management of severe TBI patients.

$Pbto_2$ Is an Independent Factor Associated With Severe TBI Outcome

Observational clinical TBI studies demonstrate a significant association between brain hypoxia and both mortality and unfavorable outcome.[4-6,24] Only 1 study, however, found that brain hypoxia was associated with outcome independently of elevated ICP. We found that brain hypoxia was strongly associated with an unfavorable short-term outcome regardless of high ICP and low CPP and independently of important clinical prognostic determinants (ie, age, admission GCS, Marshall CT classification, and APACHE II score; see Table 6). In addition, our data suggest that after severe TBI, $Pbto_2$ levels may be a better physiological variable to predict outcome than ICP or CPP in some patients.

The Role of ICP and CPP

Intracranial pressure monitors are the "gold standard" used to monitor patients with severe TBI. There is a well-described relationship between mortality and high ICP (> 20 mm Hg) after severe TBI; however, the effectiveness of ICP-guided care has yet to be confirmed in a clinical trial, and 1 retrospective study suggests that some patients may not benefit from ICP-targeted therapy.[25] Similarly, CPP-based care does not always improve outcome because therapies to maintain CPP > 70 mm Hg may be associated with lung injury.[26] Consequently, the optimal CPP treatment threshold remains unclear. Current severe TBI management guidelines recommend a CPP between 50 and 70 mm Hg.[16] In this study, the threshold for low CPP was set at 60 mm Hg to reflect these recommendations and our local practices for CPP management. A CPP threshold between 50 and 70 mm Hg may not be sufficient to prevent cerebral hypoxia/ischemia in all TBI patients.[27] In addition, how CPP is managed, eg, the Lund concept, may affect whether there is secondary injury. This has led to the concept of individualized CPP management, guided by CPP-correlated variations of $Pbto_2$ in the early phase after TBI.[28] In the present study, several observations lend support to a management strategy of "individualized CPP and $Pbto_2$–guided care"[28]: (1) Normal ICP and CPP after severe TBI do not always exclude brain hypoxia; (2) although a CPP decrease is a common cause of brain hypoxia, CPP was ≥ 60 mm Hg in approximately half of brain hypoxic time, suggesting that the CPP threshold for brain hypoxia varies widely between individual subjects; (3) other factors (ie, low Pao_2, low hemoglobin concentration, hyperthermia, induced cooling) can cause brain hypoxia; (4) although elevated ICP alone is associated with unfavorable outcome,[7,8] this association loses independent prognostic significance when ICP is controlled for $Pbto_2$; and (5) low CPP < 60 mm Hg is associated with unfavorable outcome only when it occurs simultaneously with brain hypoxia. These findings have 2 important clinical implications: $Pbto_2$ may be a better physiological marker of TBI outcome than ICP and CPP in some patients, and low CPP is not detrimental per se but may be detrimental when it causes brain hypoxia. Our data do not imply that an ICP monitor or ICP/CPP treatment is not needed after TBI. Ideally, all 3 parameters should be monitored because elevated ICP or low CPP may be one cause of reduced $Pbto_2$, as was the case in many patients in our study (Table 3). The use of a $Pbto_2$ monitor should complement an ICP monitor, and if data from several monitors are synthesized, then therapy may be targeted to patient-specific pathophysiology. We and others have demonstrated that $Pbto_2$ data also may help to target other therapies, eg, red blood cell transfusion[29,30] or treatment of elevated ICP,[31-34] or to guide individual CPP management, thereby limiting secondary brain hypoxic insults.[28,35,36] Although these findings support the concept of incorporating $Pbto_2$ data into clinical management strategies, the literature on the impact of $Pbto_2$-directed therapy on outcome is conflicting.[37-40] Randomized trials therefore are required to define whether a $Pbto_2$-directed strategy improves outcome after severe TBI.

Methodological Limitations

Our study has several potential limitations. First, the data were examined retrospectively, and this may bias our results. However, the data were collected prospectively and analyzed with linear interpolation methods to calculate total time of brain hypoxia and with robust statistical methods. In particular, when the impact of physiological parameters on outcome is assessed, the use of linear interpolation method to calculate the total time of physiological abnormalities provides greater insight into the relationship than simply calculation of absolute mean or median values.[17,41] Thus, we believe that the method used strengthens the main findings of our study. Second, the study was performed on patients treated at a single institution, so it may lack external validity. However, each patient was treated according to a standardized protocol consistent with the Guidelines for Severe Traumatic Brain Injury used in most level 1 trauma centers, and therapeutic intensity level was assessed. Third, we analyzed short-term outcome because only 30-day outcome was collected prospectively in this data set. This time point is valid for analysis of ICU processes of care such as ours. Although this time point may be sufficient to differentiate outcomes of general ICU patients, it may not be sufficient to reflect TBI recovery when functional outcome is more important and can occur with time. Fourth, the duration of monitoring differed among patients. This may be a potential confounding variable with an effect in both directions. However, the duration of monitoring was similar between patients with favorable or unfavorable outcome. In addition, when analysis was limited to the first 24 hours, the relationship between brain hypoxia and poor outcome remained. These findings suggest that duration of monitoring may not influence our results. Fifth, the sample size and number of events per predictor in the final statistical model are relatively small. This may mean that some important variables are excluded or are relevant only in our particular cohort of patients. In addition, the small sample size limits an investigation between variables. For that reason, we can conclude only that brain hypoxia appears to be an independent factor associated with poor short-term outcome. Sixth, the $Pbto_2$ monitor we used samples a limited volume of tissue around its tip; ie, it measures regional $Pbto_2$ and may not always reflect global brain oxygenation. Similarly, ICP monitors (and so CPP measurements) also may be considered "local" monitors in some patients[42]; ie, global intracranial physiology may be difficult to monitor precisely with current intracranial monitors. However, clinical studies suggest that regional $Pbto_2$ reflects global brain tissue oxygenation when the monitor is located in uninjured brain,[43,44] as in the present study. Importantly, with the monitor system we used, the ICP and $Pbto_2$ monitors are virtually in the same location; thus, the 2 data points likely reflect the same underlying pathology. Seventh, the $Pbto_2$ probes were placed in normal-appearing brain tissue on admission CT, not in pericontusional areas. This may have led to an underestimate of the extent of brain hypoxia, at least in patients with focal injury.[45] In addition, outcome may depend in part on where the probe is located relative to pathology. Eighth, the main determinants of

$Pbto_2$ in humans are only beginning to be elucidated. Whether $Pbto_2$ reflects oxygen diffusion, oxygen extraction, or oxygen accumulation in the brain[46-48] remains unknown. It appears, however, that $Pbto_2$ is not simply a measure of cerebral blood flow.[49] We did not measure cerebral blood flow, oxygen extraction fraction, or cerebral metabolic rate of oxygen; thus, we cannot comment on why brain hypoxia developed and whether/which underlying causes are associated with outcome. Because CPP augmentation may improve $Pbto_2$ in some patients,[36] it is likely that $Pbto_2 < 15$ mm Hg represents cerebral ischemia, at least under certain conditions in some patients. Finally, there are several reported thresholds for brain hypoxia or when to initiate therapy for brain hypoxia. Because the main purpose of the present study was to analyze the impact of brain hypoxia on short-term outcome, we chose a threshold of $Pbto_2 < 15$ mm Hg, consistent with the present definitions of brain tissue hypoxia from the Brain Trauma Foundation guidelines.[2] It is conceivable that the results may be different if different thresholds were used, but we think this is unlikely on the basis of the experience with brain oxygen monitors in TBI to date.[12] The present study also is not a pure observational study because we treated brain oxygen when it was < 20 mm Hg. and how a patient responds to therapy may influence outcome.[12] Our results therefore may be interpreted to mean that those patients who do not respond to therapy to correct $Pbto_2$ are likely to do poorly rather than that the total burden of brain hypoxia is associated with outcome.

CONCLUSION

Brain hypoxia ($Pbto_2 < 15$ mm Hg) is frequent in patients with severe TBI, and although it may be caused by a decrease in CPP or an increase in ICP, brain hypoxia also occurs in patients in whom ICP and CPP are normal. Furthermore, the CPP threshold for brain hypoxia varies widely between subjects, and $Pbto_2$ may be < 15 mm Hg despite CPP being ≥ 60 mm Hg. In our patient cohort, brain hypoxia was associated with an unfavorable short-term outcome independently of elevated ICP, low CPP, and the severity of cerebral and systemic injury. Our data suggest that $Pbto_2$ is an important physiological target after severe TBI to complement ICP and CPP and to help guide the management of TBI patients. Further studies are needed to examine whether $Pbto_2$-directed therapy improves outcome in patients with severe TBI.

Disclosures

Eileen Maloney-Wilensky and Peter D. LeRoux are members of Integra Lifesciences Speaker's Bureau. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

Oddo et al make a clear case in this article that brain hypoxia, as defined by low brain tissue oxygen tensions, is associated with poorer short-term outcome in severe traumatic brain injury (TBI). The number of hypoxic episodes and summated duration of these episodes were shown to be independent predictors of unfavorable outcome as assessed by the Glasgow Outcome Scale at 30 days after injury. A major asset of this article is its clarity of presentation. This clarity, however, has come at a certain cost and necessitated perhaps an overly simplistic approach to the analysis of an extremely complex problem.

Confounding factors influencing the interpretation of the findings reported by Oddo et al lie particularly in the variability of duration of monitoring and the fact that treatment intensity was not reported. Taking these factors into consideration would necessitate a much more sophisticated approach to the statistical analysis. It may be argued that the finding of an increased duration of adverse episodes (low brain tissue Po_2, high intracranial pressure [ICP], or low cerebral perfusion pressure [CPP]) in patients with poorer outcome might simply be interpreted as identifying nonresponders to treatment. This criticism is relevant because the treatment protocol for severe TBI as implemented in the study center included treatment of low $Pbto_2$, high ICP, and low CPP. I recall the barbiturate story in which Eisenberg et al[1] clearly showed that patients with elevated ICP responding to barbiturate administration have a much better outcome than patients not responding. The provision of summary information on the therapeutic intensity level for ICP as given in this study does not permit identification of responders versus nonresponders. From both a scientific and a clinical perspective, reporting the number, type, and success of treatment modalities used when adverse episodes were detected would have provided great additional value. Such data might also have served to further support the concept that treatment of low brain tissue Po_2 is likely to improve outcome. As a consequence, despite the clear demonstration of an independent association between brain hypoxia and unfavorable short-term outcome in TBI, we are left with some degree of uncertainty concerning cause and effect. Although I would agree with the final statement in the conclusions that ''[f]urther studies are needed to examine whether $Pbto_2$-directed therapy improves outcome in patients with severe TBI,'' the evidence pointing in this direction is definitely accumulating.

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