Conventional neurocritical care and cerebral oxygenation after traumatic brain injury

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Object. Control of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) is the foundation of traumatic brain injury (TBI) management. In this study, the authors examined whether conventional ICP- and CPP-guided neurocritical care ensures adequate brain tissue O\(_2\) in the first 6 hours after resuscitation.

Methods. Resuscitated patients with severe TBI (Glasgow Coma Scale score ≤ 8 and Injury Severity Scale score ≥ 16) who were admitted to a Level I trauma center and who underwent brain tissue O\(_2\) monitoring within 6 hours of injury were evaluated as part of a prospective observational database. Therapy was directed to maintain an ICP of 25 mm Hg or less and a CPP of 60 mm Hg or higher.

Data from a group of 25 patients that included 19 men and six women (mean age 39 ± 20 years) were examined. After resuscitation, ICP was 25 mm Hg or less in 84% and CPP was 60 mm Hg or greater in 88% of the patients. Brain O\(_2\) probes were allowed to stabilize; the initial brain tissue O\(_2\) level was 25 mm Hg or less in 68% of the patients, 20 mm Hg or less in 56%, and 10 mm Hg or less in 36%. Nearly one third (29%) of patients with ICP readings of 25 mm Hg or less and 27% with CPP levels of 60 mm Hg or greater had severe cerebral hypoxia (brain tissue O\(_2\) ≤ 10 mm Hg). Nineteen patients had both optimal ICP (< 25 mm Hg) and CPP (> 60 mm Hg); brain tissue O\(_2\) was 20 mm Hg or less in 47% and 10 mm Hg or less in 21% of these patients. The mortality rate was higher in patients with reduced brain tissue O\(_2\).

Conclusions. Brain resuscitation based on current neurocritical care standards (that is, control of ICP and CPP) does not prevent cerebral hypoxia in some patients. This finding may help explain why secondary neuronal injury occurs in some patients with adequate CPP and suggests that the definition of adequate brain resuscitation after TBI may need to be reconsidered.

KEY WORDS • traumatic brain injury • conventional care • brain oxygen • intracranial pressure

TRAUMATIC brain injury is a leading cause of death and disability among young people in the US. Increased ICP is common among patients who have a poor outcome.\(^5,13,47-49\) Consequently, current TBI management\(^1,8\) emphasizes control of ICP, in large part to maintain CPP, which is defined as MABP-ICP. Cerebral perfusion pressure is a major variable that influences cerebral blood flow, which, when inadequate, can contribute to cerebral ischemia. This increases the risk of poor outcome after TBI.\(^7,34,39,49\) Nevertheless, cerebral infarction can occur despite normal ICP and CPP.\(^35,62\) Recent positron emission tomography studies performed in humans after TBI also support the suggestion that mechanisms other than simple perfusion-limited ischemia may be responsible for cerebral hypoxia.\(^43\)

These results may help explain why therapies to improve CPP have not improved the outcome after TBI.\(^16,42-49\)

In the patients with multiple injuries and TBI, the initial care is focused on resuscitation, which is defined as adequate oxygenation to meet tissue O\(_2\) requirements. At present, successful resuscitation after trauma is confirmed by restoration of normal blood pressure, heart rate, and urine output.\(^3\) However, even when these traditional resuscitation parameters are normal, many severely injured trauma patients still have evidence of inadequate tissue oxygenation.\(^1,31\) These findings suggest that there is a need for better markers of adequate resuscitation.\(^58\) In TBI, adequate brain resuscitation is primarily defined by a CPP of 60 mm Hg or higher and an ICP of 25 mm Hg or less. In recent years direct brain tissue O\(_2\) monitoring has been demonstrated to be reliable and safe in brain-injured patients.\(^20,21,27,29,30,61,62\) In this study we used brain tissue O\(_2\) monitors to examine whether adequate brain resuscitation, defined by ICP and CPP, ensured adequate cerebral oxygenation after patients with TBI were resuscitated.

Abbreviations used in this paper: CPP = cerebral perfusion pressure; CT = computed tomography; GCS = Glasgow Coma Scale; ICP = intracranial pressure; ISS = Injury Severity Scale; MABP = mean arterial blood pressure; TBI = traumatic brain injury.
Clinical Material and Methods

Patient Population

Patients with multiple trauma (ISS score ≥ 16) and severe TBI (GCS score ≤ 8) who were admitted within 3 hours of injury to the Hospital of the University of Pennsylvania, a Level I trauma center, and in whom ICP and brain tissue O₂ monitoring were begun within 6 hours of injury were considered for this study. The time of injury was based on the time of the initial call to the Emergency Medicine Services. Patients were evaluated as part of an observational prospective database with Institutional Review Board approval. Patients who had suffered cranial gunshot wounds or other penetrating cranial injuries, ongoing blood loss, or whose postresuscitation systolic blood pressure was less than 90 mm Hg, arterial saturation of O₂ was less than 93%, or in whom pupils were fixed and dilated bilaterally were excluded from analysis. Severe TBI was determined by a history of trauma, a clinical examination resulting in a postresuscitation GCS score of 3 to 8, and a head CT scan confirming that there was no other cause for their coma.

Brain Monitors

The ICP, brain temperature, and brain tissue O₂ were continuously monitored using commercially available products (LICOX; Integra LifeSciences, Plainsboro, NJ). The CPP was calculated from the measured parameters (CPP = MABP - ICP). Once the patients had been resuscitated, the intracranial monitors (for ICP, brain temperature, and brain tissue O₂) were inserted through a bur hole into the frontal lobe and adjacent to the worst area of injury observed on admission head CT scans. The heart rate, blood pressure (through an arterial line), and arterial saturation of O₂ were also recorded in all patients. All physiological variables were continuously recorded using a bedside monitor (Component Monitoring System M1046-9090C; Hewlett Packard, Andover, MA). Immediately after insertion, brain tissue O₂ parameters can be abnormal. Therefore, for data analysis, the 1st hour after insertion was excluded to allow for probe stabilization. Probe function and stability were confirmed by an appropriate increase in brain tissue O₂ after an FiO₂ challenge (FiO₂ 1.0). Follow-up head CT scans were obtained in all patients within 24 hours of admission; this confirmed correct placement of the various monitors, for example, not in a contusion or infarct.

Management of TBI

Patients underwent intubation and mechanical ventilation, and were resuscitated according to the Advanced Trauma Life Support Course. This included hemostasis, colloid or crystalloid administration to restore MABP to greater than 90 mm Hg, and blood transfusion to restore adequate hemoglobin. Hypertonic saline was not used for resuscitation. Eligible patients were admitted to the Neurosurgical Intensive Care Unit or the Surgical and Trauma Intensive Care Unit at our institution and their condition managed according to current severe TBI guidelines. Briefly, this included the following: 1) early identification and evacuation of traumatic hematoma; 2) intubation and ventilation to maintain PaCO₂ between 30 and 40 mm Hg; 3) sedation using propofol or fentanyl during the first 24 hours; 4) bed rest with the head of the bed maintained between 15 and 30°; 5) normothermia (~35–37°C); 6) euvolemia attained using a baseline crystalloid infusion (0.9% normal saline, 20 mEq/L KCl; 80–100 ml/hour); and 7) anticonvulsant medications (Dilantin).

Management of ICP and CPP

Patients received mannitol (0.5–1 g/kg) for ICP greater than 20 mm Hg for more than 2 minutes, to a serum osmolality of 315 mOsm. A ventriculostomy was placed when mannitol failed to reduce increased ICP. Thereafter, optimized hyperventilation (PaCO₂ ~ 30 mm Hg), additional propofol, or pentobarbital-induced burst suppression was administered or a decompressive hemicraniectomy considered if ICP remained elevated. To maintain CPP (> 60 mm Hg), crystalloid was infused if the ICP allowed, or phenylephrine (10–100 μg/minute) was administered when the serum lactate level was not elevated.

Results

Patient Characteristics

Twenty-five resuscitated patients in whom a brain O₂ monitor was placed within 6 hours of TBI and who were identified during an 18-month period were examined for this study. There were 19 men and six women with a mean age of 39 ± 20 years. Their median admission ISS score was 29 (range 17–50). The postresuscitation GCS score was 3 in 15 patients, 4 to 6 in eight patients, and 7 to 8 in two patients. All patients had closed head injuries (Table 1).

Mean ICP and CPP

We compared the mean ICP, CPP, and brain tissue O₂ obtained during the 1-hour period after brain tissue O₂ probe stabilization. (All values are given as the mean ± standard deviation.) The mean ICP and CPP in the initial hour of brain tissue O₂ monitoring following probe stabilization were 17 ± 9 and 68 ± 11 mm Hg, respectively (Fig. 1). In 21 patients (84%, Group A), ICP was 25 mm Hg or less (mean 15 ± 6 mm Hg; Fig. 2 upper). Twenty-two patients (88%, Group B) had an ICP of 60 mm Hg or less (mean 71 ± 9 mm Hg; Fig. 2 upper). Nineteen patients (76%, Group C; Fig. 2 lower) had both optimal ICP (<25 mm Hg) and CPP (>60 mm Hg). During the period in which brain tissue O₂ was monitored for this study, 21 patients received propofol, and increased ICP was treated by administration of mannitol (six patients), a ventriculostomy (two), and optimized hyperventilation (one). Thirteen patients received phenylephrine or other pressors to maintain CPP.

Brain Tissue O₂

During the 1-hour period after probe stabilization, the mean brain tissue O₂ level for all 25 patients was 19.68 ± 12.57 mm Hg (Fig. 1). The mean brain tissue O₂ was 25 mm Hg or less in 17 patients (68%), 20 mm Hg or less in 14 (56%), and 10 mm Hg or less in nine (36%) during the initial hour of postinsertion brain tissue O₂ probe stabilization (Fig. 2 upper). Among the 21 patients in Group A (ICP ≤ 25 mm Hg), 12 (57%) had brain tissue O₂ levels of 25 mm Hg or less, 10 (48%) had levels of 20 mm Hg or less, and six (29%) had levels of 10 mm Hg or less during the initial hour of brain tissue O₂ monitoring following probe stabili-
lization. In the 22 Group B patients (CPP ≥ 60 mm Hg), brain tissue O₂ levels of 25 mm Hg or less were observed in 13 (59%), levels of 20 mm Hg or less were found in 11 (50%), and levels of 10 mm Hg or less were observed in six (27%; Fig. 2 upper). When optimal resuscitation according to current guidelines was achieved (ICP < 25 mm Hg and CPP > 60 mm Hg) in Group C (19 patients), the brain tissue O₂ level was 25 mm Hg or greater in nine (47%); 20 to 24 mm Hg in one (5%); 15 to 19 mm Hg in four (21%); 10 to 14 mm Hg in one (5%), and less than 10 mm Hg in four (21%; Fig. 2 lower). In the 25 patients included in this analysis, the brain O₂ level did not correlate with ICP (r² = 0.0663; Fig. 3) or CPP (r² = 0.2221).

Impact of Brain Tissue O₂ on Mortality Rate

Overall, nine patients (36%) died. Among patients whose resuscitation was optimal (ICP < 25 mm Hg and CPP > 60 mm Hg; Group C), the mortality rate was 32%. In patients whose ICP was elevated or CPP reduced, the mortality rate was 50%. The mortality rate similarly was associated with brain O₂, and among all 25 patients it was 30% when brain O₂ was greater than 25 mm Hg, 43% if the O₂ level was less than 20 mm Hg; and 50% when it was less than 15 mm Hg. When the brain tissue O₂ level was less than 20 mm Hg and did not improve during resuscitation, the mortality rate was 60%.

Discussion

In this study we examined 25 patients with multiple injuries and severe TBI in whom a brain O₂ monitor was placed within 6 hours of injury. Each patient was resuscitated according to published Advanced Trauma Life Support and TBI guidelines, that is, ICP- and CPP-directed therapy. Despite this, many still showed evidence of inadequate brain oxygenation based on brain tissue O₂ monitoring. In particular, one third of patients who received the current standard of care for adequate brain resuscitation (that is, CPP ≥ 60 mm Hg) still had evidence of severe cerebral hypoxia (brain tissue O₂ ≤ 10 mm Hg) in the early hours after TBI. The mortality rate was increased in patients with cerebral hypoxia, particularly when it did not improve during resuscitation. These results emphasize the importance of multimodality monitoring in the care of patients with severe TBI and suggest that we may need to reconsider the definition of adequate brain resuscitation.

Methodological Limitations

Brain O₂ levels in this study were measured using a commercially available monitor (LICOX). This monitor has been available for more than 15 years, and it has been in clinical use in the US since 2001. Its excellent reliability,
sensitivity error less than 1%, near zero drift, clinical usefulness, and the relationship between brain $O_2$ and outcome are well described in the literature.\textsuperscript{5,10,21,24,27,33,36,50,59–62} There are several potential limitations, however, in our study. First, the data were analyzed retrospectively from a prospective observational database. It is conceivable that management variables may have influenced the results. We think this is unlikely, however, because all patients with TBI admitted to the Hospital of the University of Pennsylvania are treated in a standardized fashion according to current TBI and Advanced Trauma Life Support guidelines.\textsuperscript{3,4,8} Second, the sample size is small, which means that our results should be regarded as preliminary. Nevertheless, the data are compelling in that one third of patients considered adequately resuscitated (CPP $\geq$ 60 mm Hg) still had evidence of severe brain hypoxia. Third, patients who underwent craniotomy for mass lesions generally did not receive a brain $O_2$ monitor within 6 hours of injury. It is possible that this may alter the results and will require further study. However, we recently observed that during the intensive care unit stay, episodes of brain hypoxia, including those among patients who have undergone craniotomy, are not associated with ICP or CPP.\textsuperscript{25} This supports the suggestion that the results of our study may also apply during the initial resuscitation of patients who require craniotomy after TBI. Fourth, the brain tissue monitor we used records local brain tissue $O_2$ within white matter. The most profound metabolic abnormalities are found regionally around contusions, so we tried to place the probes close to the worst area of injury observed on admission head CT scans.\textsuperscript{52} Each patient underwent a head CT scan following brain tissue $O_2$ monitor placement to confirm that the probe was located in “normal” white matter (that is, tissue free of infarct or contusion). When a brain tissue $O_2$ monitor is placed in

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“undamaged” brain areas, the values also can be extrapolated to evaluate global oxygenation even though the probe only measures local brain tissue \( \text{O}_2 \). Fifth, the \( \text{O}_2 \) probe is subject to a so-called insertion effect. To avoid this, the probes were allowed to stabilize for 1 hour and their function was then confirmed with an \( \text{O}_2 \) challenge. Finally, brain tissue \( \text{O}_2 \), like cerebral blood flow, \( 7,42,60–62 \) may change over time after severe TBI. In addition, outlier values or hour-to-hour variability in the brain tissue \( \text{O}_2 \) level may influence the results. We think this is unlikely because all values obtained during the hour after brain tissue \( \text{O}_2 \) probe stabilization were averaged and the mean or median was used in analysis. This may be important because cerebral hypoxia that lasts longer than 30 minutes is a significant factor in poor outcome.\(^5\)

**Resuscitation After Severe Trauma**

The goal of resuscitation after trauma is to restore and maintain adequate oxygenation to meet tissue requirements. However, the ideal measure of adequate brain resuscitation after TBI does not exist at present. Similarly, the gold standard for systemic resuscitation, including restoration of normal pulse rate, blood pressure, and urine output,\(^7\) may be insufficient in many patients with severe trauma because evidence for inadequate tissue oxygenation, measured by lactate, gastric tonometry, or cardiac function, among others, may still be present in some patients.\(^1,2,41,44,51\) Consequently, Fiddian-Green, et al.,\(^22\) have suggested that increased delivery “D” and extraction “E” of \( \text{O}_2 \) be added to the traditional “ABCs” of resuscitation. Several but not all studies support the hypothesis that this concept of resuscitation to maximize optimal tissue \( \text{O}_2 \) may reduce the mortality rate and the incidence of major organ dysfunction in the severely injured patient\(^{6,45,53,54,60}\). It is clear from these studies that the greatest benefit is observed in the sickest patients and in those in whom oxygenation is initiated early during resuscitation.\(^7,22,53,54\) The relationship between early “neuroprotection,” both in laboratory and clinical studies, and prevention of secondary brain injury is well known. Based on the results of our study we would suggest that, despite adequate early resuscitation after TBI according to present gold standards (that is, ICP and CPP), one third of patients still have evidence of inadequate brain resuscitation (that is, cerebral hypoxia).

**Brain \( \text{O}_2 \) Levels After TBI**

Several converging lines of evidence support the suggestion that brain tissue \( \text{O}_2 \) monitoring is a safe, sensitive, and reliable diagnostic tool and may be an ideal complement to ICP monitors.\(^21,33,36,61,62\) In particular, in recent studies investigators have demonstrated that cerebral hypoxia, which is common after severe TBI even when CPP is normal, is a key factor that leads to secondary brain damage and poor outcome after TBI.\(^10,21,23,24,36,42,50,55,59–62\) Brain \( \text{O}_2 \) values between 20 and 40 mm Hg are regarded as normal, whereas reductions of less than 10 to 15 mm Hg are associated with cerebral ischemic injury. In addition, poor outcome is associated with the number, duration, and intensity of cerebral hypoxic episodes (brain tissue \( \text{O}_2 < 15 \text{ mm Hg} \)), and any brain tissue \( \text{O}_2 \) values of 5 mm Hg or less.\(^5,21,28,36,53,59–62\) From these various results we can infer that knowledge about brain oxygenation may be important in resuscitation and care of the patient with TBI. Whether improved brain \( \text{O}_2 \) will make a difference in outcome remains unclear. We have observed that therapy directed to maintaining a brain tissue \( \text{O}_2 \) level greater than 20 mm Hg reduces the mortal-

**FIG. 3.** Scattergram demonstrating the relationship between ICP and brain tissue \( \text{O}_2 \) levels (\( r^2 = 0.0663 \)). The ICP and brain \( \text{O}_2 \) values represent the mean of each patient’s values obtained during the first 1-hour period after brain tissue \( \text{O}_2 \) probe stabilization.
ity rate after severe TBI.\textsuperscript{48} However, if therapy to increase brain O\textsubscript{2} levels is delayed until there is severe hypoxia (brain tissue O\textsubscript{2} \textless 10 mm Hg),\textsuperscript{42} the outcome is not improved.

**Effect of CPP and Brain Tissue O\textsubscript{2} Levels After TBI**

The goal of current TBI management is to reduce ICP and optimize CPP to prevent cerebral ischemia,\textsuperscript{43,48} which exacerbates TBI outcome.\textsuperscript{26,31,39,49} The adverse effects of fail-

ure to maintain an adequate CPP or to reduce elevated ICP after TBI are also well documented.\textsuperscript{13,38} Nevertheless, increased ICP is responsible for less than half of the episodes of cerebral ischemia,\textsuperscript{24} and cerebral infarction can occur despite normal ICP and CPP.\textsuperscript{35,62} Furthermore, CPP-directed therapies have not improved outcome after TBI.\textsuperscript{16,49} The critical threshold for CPP appears to be 60 mm Hg.\textsuperscript{12,15,30,33} Although an adequate CPP is important, another important factor may be adequate resuscitation (that is, fluid balance and tissue oxygenation). For example, in a post hoc analy-

sis of the National Acute Brain Injury Study: Hypothermia randomized trial, Clifton, et al.,\textsuperscript{15} observed that among other variables, fluid balance, CPP less than 60 mm Hg, and ICP greater than 25 mm Hg were important factors associated with outcome. After stepwise logistic regression was performed, the variables associated with poor outcome were admission GCS score, age, MABP less than 70 mm Hg, lowest quartile fluid balance, and ICP greater than 25 mm Hg, suggesting that adequate resuscitation (that is, fluid bal-

ance) rather than adequate CPP alone may be important to brain recovery. Similarly, our findings raise the question of what defines adequate resuscitation of the brain after TBI. Rather than rely on a hydraulic measure (CPP and ICP), a definition similar to that suggested for shock\textsuperscript{58} that regards resuscitation as complete when the O\textsubscript{2} debt is eliminated and normal aerobic metabolism is restored may need to be considered.

Does an adequate CPP mean adequate brain O\textsubscript{2} levels? In a small study of 11 patients, Murr and Schurer\textsuperscript{46} observed a relationship between CPP (alterations in MABP and ICP) and jugular saturation of O\textsubscript{2}. By contrast, Cruz, et al.,\textsuperscript{19} in a study that included 66 patients, found no relationship between CPP and arteriovenous difference of O\textsubscript{2} when CPP was in the normal range. Chan, et al.,\textsuperscript{11} observed that a CPP less than 70 mm Hg is associated with a reduction in jugular saturation of O\textsubscript{2}. The correlation was absent when CPP was greater than 70 mm Hg. There are many problems with retrograde jugular catheters, and up to 50% of readings may be inaccurate.\textsuperscript{14} However, the relationship between brain tis-

sue O\textsubscript{2} and CPP has been examined in only a few studies in which direct brain O\textsubscript{2} monitoring was used.\textsuperscript{50,53,57} In their study of 21 patients, Kiening, et al.,\textsuperscript{53} observed that increasing CPP from 32 ± 2 to 67 ± 4 mm Hg improved brain tissue O\textsubscript{2} levels by 62%, and that increasing CPP higher than 68 mm Hg did not lead to further improvement in brain O\textsubscript{2} levels. Stochetti, et al.,\textsuperscript{57} also observed that increasing CPP could increase brain O\textsubscript{2} levels, although low brain tissue O\textsubscript{2} could be associated with normal CPP. Based on our results, we suggest that in patients with TBI who receive ICP- and CPP-directed therapy, severe cerebral hypoxia (brain tissue O\textsubscript{2} \textless 10 mm Hg) can be detected in nearly one third of pa-

tients when CPP is adequate. This observation may in part explain why Cruz,\textsuperscript{19} in a prospective study of 353 patients, found that monitoring and management of CPP alone after TBI may be insufficient. He found that the 6-month out-

come was better in the patients who also had monitoring and management of cerebral O\textsubscript{2} extraction than in those who just underwent CPP-based therapy. We also recently found that a brain tissue O\textsubscript{2} monitoring and management strategy halved the mortality rate when compared with an ICP- and CPP-based strategy.\textsuperscript{56}

**Conclusions**

How best to resuscitate the patient with multiple injuries and severe TBI is not fully defined. It is clear that the risks and benefits of fluid resuscitation with crystalloid or colloid solutions are finely balanced.\textsuperscript{16,37,49,58} In addition, in some patients with trauma, blood may be deleterious.\textsuperscript{48} The role of alternate resuscitation strategies such as hypertonic saline,\textsuperscript{17,64} hypertensive resuscitation,\textsuperscript{37,58} or norepinephrine to increase CPP\textsuperscript{16,34,49} will need further analysis. The difficulty may not be what is used but rather what defines the end point of resuscitation. Based on our results, we suggest that as new information calls current CPP management into question\textsuperscript{16,49} we need to identify better end points of resusci-

tation. One potential end point may be brain O\textsubscript{2} levels. Such a definition would be consistent with current thinking about resuscitation for shock.\textsuperscript{58} We suggest that brain tissue O\textsubscript{2}–guided management will determine the appropriate CPP for each patient, thus avoiding the potentially deleterious effects of efforts to increase CPP in all patients.\textsuperscript{16,49} In addition, rather than base assessments of adequate brain resus-

citation on hydraulic measures (ICP and CPP) alone, we believe that brain tissue O\textsubscript{2}–guided management is a first and necessary step in defining better metabolic end points of adequate brain resuscitation after TBI.

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