

Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring

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Object. An intracranial pressure (ICP) monitor, from which cerebral perfusion pressure (CPP) is estimated, is recommended in the care of severe traumatic brain injury (TBI). Nevertheless, optimal ICP and CPP management may not always prevent cerebral ischemia, which adversely influences patient outcome. The authors therefore determined whether the addition of a brain tissue oxygen tension (PO₂) monitor in the treatment of TBI was associated with an improved patient outcome.

Methods. Patients with severe TBI (Glasgow Coma Scale [GCS] score < 8) who had been admitted to a Level I trauma center were evaluated as part of a prospective observational database. Patients treated with ICP and brain tissue PO₂ monitoring were compared with historical controls matched for age, pathological features, admission GCS score, and Injury Severity Score who had undergone ICP monitoring alone. Therapy in both patient groups was aimed at maintaining an ICP less than 20 mm Hg and a CPP greater than 60 mm Hg. Among patients whose brain tissue PO₂ was monitored, oxygenation was maintained at levels greater than 25 mm Hg. Twenty-five patients with a mean age of 44 ± 14 years were treated using an ICP monitor alone. Twenty-eight patients with a mean age of 38 ± 18 years underwent brain tissue PO₂-directed care. The mean daily ICP and CPP levels were similar in each group. The mortality rate in patients treated using conventional ICP and CPP management was 44%. Patients who also underwent brain tissue PO₂ monitoring had a significantly reduced mortality rate of 25% (p < 0.05).

Conclusions. The use of both ICP and brain tissue PO₂ monitors and therapy directed at brain tissue PO₂ is associated with reduced patient death following severe TBI.

KEY WORDS • brain tissue oxygenation • intracranial pressure • traumatic brain injury • intracranial pressure monitoring • mortality rate

TRAUMATIC brain injury is a leading cause of death and disability among young people in the US. In particular, among patients with concomitant TBI and elevated ICP, death or a poor outcome is commonplace.^{6,27,29,33,35} Current management of severe head injury is therefore centered on the reduction of elevated ICP, which is observed in more than half of the patients with TBI.^{3,6,36,37} The primary reason for treating increased ICP is to maintain CPP and thus prevent cerebral ischemia and infarction, which otherwise commonly occur in patients with TBI who die.¹⁶ Note, however, that results of several studies have demonstrated that cerebral infarction can occur despite normal ICP and CPP and that not all episodes of cerebral ischemia are associated with elevated ICP.^{13,24,48,49} These data, therefore, indicate the necessity of measuring more than ICP and CPP to best treat patients with severe TBI.

An ICP monitor, from which CPP is estimated, repre-

sents the present gold standard in intracranial monitoring for severe TBI. Several converging lines of evidence indicate that the continuous measurement of local brain tissue PO₂ is a useful complement to ICP monitoring in severe TBI therapy.^{4,10,11,15,17,19,23,43,45–47} This theory makes intuitive sense given that the brain is highly dependent on a continuous supply of O₂ to maintain cellular integrity.⁵⁰ In particular, several investigators have described a significant relationship between poor patient outcome and the number, duration, and intensity of cerebral hypoxia episodes (brain tissue PO₂ < 15 mm Hg).^{1,11,23,47,48} Authors of these studies did not definitively determine whether treatment of cerebral hypoxia was associated with better outcome, however.

No clinical trial data have demonstrated that the use of an ICP monitor is associated with better patient outcome after TBI, although authors of several clinical series have posited that such is the case.^{2,3,12,20,27} Similarly, it is unclear whether a treatment policy that includes brain tissue PO₂ monitoring promotes a better outcome after severe TBI. We therefore undertook the present study in which historical controls were used to compare TBI management strategies consisting of ICP monitoring alone or both ICP and brain tissue PO₂ monitoring. The primary objective of our analysis was

Abbreviations used in this paper: CPP = cerebral perfusion pressure; CT = computerized tomography; GCS = Glasgow Coma Scale; HUP = Hospital of the University of Pennsylvania; ICP = intracranial pressure; ICU = intensive care unit; ISS = Injury Severity Score; SaO₂ = arterial O₂ saturation; TBI = traumatic brain injury.

to determine whether the patient mortality rate was reduced when a brain tissue PO₂ monitor was used to guide treatment of TBI.

Clinical Material and Methods

Patient Population

Patients with severe TBI who had been admitted to the HUP, a Level I trauma center, between January 2000 and July 2002 were considered for inclusion in this study. Patients were evaluated as part of an observational prospective database with Institutional Review Board approval. Inclusion criteria consisted of an admission GCS score less than 8 and an ISS of 16 or more following initial emergency room resuscitation after head injury. Patients suffering from cranial gunshot wounds or other penetrating injuries, those whose postresuscitation systolic blood pressure was less than 90 mm Hg and their SaO₂ was less than 93%, or those who had bilateral fixed and dilated pupils were excluded from analysis. Direct brain tissue PO₂ monitoring was first introduced to the HUP in July 2001. We therefore identified two groups of patients whose only treatment variable was the use of brain tissue PO₂ monitoring to guide therapy and cerebral resuscitation. Group A consisted of patients who had been treated using an ICP monitor for ICP/CPP-directed therapy. Group B consisted of patients who had been cared for using both an ICP and a brain tissue PO₂ monitor for brain tissue PO₂-directed management. The patients were matched for age, admission GCS score, ISS, and pathological features. To avoid potential treatment biases that can occur during the months immediately before and after the introduction of a new technology, patients treated in the 3 months before or after the introduction of brain tissue PO₂ monitoring were not considered for analysis.

Patient Monitoring

Patients were cared for in the neurosurgical ICU. Each patient in Group A was monitored using an ICP monitor (Camino; Integra NeuroSciences, Plainsboro, NJ) inserted through a frontal burr hole. Patients in Group B were monitored using ICP and brain tissue PO₂ and temperature probes inserted through a triple-lumen bolt (LICOX CMP Triple Lumen Monitoring System; Integra NeuroSciences) into a frontal burr hole. The monitors in all patients were placed into healthy brain tissue on the side with maximal pathological features or swelling, according to admission CT scanning studies. Correct placement of the various monitors—for instance, not in a contusion or infarct—was confirmed on follow-up CT scanning. All patients were monitored for at least 72 hours unless care was withdrawn or the patient died. The ICP monitor was removed only when ICP had been normal for 24 hours without treatment. Heart rate, blood pressure through an arterial line, and SaO₂ were recorded in all patients. All physiological variables were continuously recorded using a bedside monitor (Component Monitoring System, M1046-9090C; Hewlett Packard, Andover, MA).

Management of TBI

Group A patients (ICP/CPP-guided therapy) were treated according to published recommendations for severe

TBI,^{4,5,36,37} which included early evacuation of mass lesions and a stair-step approach to elevated ICP. The treatment goal in this patient group was aimed at keeping ICP less than 20 mm Hg and CPP greater than 60 mm Hg. Each patient was fully resuscitated, intubated, and received mechanical ventilation with the head of the bed initially elevated approximately 20 to 30°. Ventilation was adjusted to maintain PCO₂ at approximately 35 mm Hg and SaO₂ greater than 93%. Patients received intravenous administration of morphine or fentanyl and were sedated using a propofol infusion. When ICP became elevated, defined as a level greater than 20 mm Hg for more than 5 minutes, intravenous boluses of mannitol (1–2 g/kg) were administered to the patient. Following adequate fluid resuscitation, phenylephrine (10–100 µg/minute) was administered when CPP was 60 mm Hg or less for longer than 15 minutes. If ICP remained elevated despite mannitol infusions, an external ventricular drain was placed for cerebrospinal fluid drainage and the patient was paralyzed using pancuronium. Additional mannitol boluses were administered if ICP remained elevated despite these strategies, until a maximal serum osmolarity of 320 mOsm was measured. Optimized hyperventilation guided by a jugular bulb catheter was initiated as a second-tier therapy when sedation, paralysis, osmotherapy, and external ventricular drain placement failed to reduce ICP. Hyperventilation was increased to a PaCO₂ of 25 mm Hg while maintaining a jugular venous O₂ saturation greater than 55%. When hyperventilation was required for more than 24 hours or did not reduce ICP, barbiturate agents (a bolus dose followed by continuous infusion) were administered to induce electroencephalography-monitored burst suppression. In these patients vasopressor agents were administered to maintain adequate CPP if there was barbiturate-associated hypotension. A large decompressive hemicraniectomy was performed using previously reported techniques^{42,44} when ICP was persistently greater than 20 mm Hg despite maximal medical management.

Group B patients (PO₂-guided therapy) had ICP and CPP treatment goals and care similar to those in Group A. Note, however, that patients in Group B had an additional treatment parameter, that is, to maintain brain tissue PO₂ at a level greater than or equal to 25 mm Hg. This management method was cause-directed. Initial intervention involved increasing CPP to improve brain tissue PO₂ and an O₂ challenge (100% fraction of inspired O₂). If there was no improvement in brain tissue PO₂, a head CT scan was obtained to determine the correct position of the PO₂ monitor and whether delayed hemorrhage or another pathological entity had developed. Pulmonary or ventilation-associated reductions in brain tissue PO₂ were assessed and corrected. Then, metabolic delivery (for example, volume status or mean arterial blood pressure) or demand (for instance, pain, fever, or seizures) abnormalities were corrected. If these measures failed, a blood transfusion was performed to achieve a hemoglobin level of 10 mg/dl. When a reversible parameter (such as increased ICP, hypotension, airway obstruction, pulmonary edema, fever, seizures, and so forth) was not identified, fraction of inspired O₂ was titrated to achieve a brain tissue PO₂ of at least 25 mm Hg. In addition, Group B patients underwent decompressive hemicraniectomy when brain tissue PO₂ progressively declined or was less than or equal to 20 mm Hg for longer than 15 minutes despite maximal medical therapy for elevated ICP.

Reduction in mortality rate through brain tissue PO₂ management

TABLE 1

*Clinical characteristics in 53 patients who underwent ICP/ CPP-based therapy or combined ICP/ CPP and brain tissue PO₂-based therapy**

Characteristic	Group A (ICP/ CPP)	Group B (brain tissue PO ₂)
sex (male/female)	17:8	25:3
mean age (yrs)	44 ± 14	38 ± 18
median ISS (range)	26 (17–45)	27 (17–50)
pathological entity†		
CHI/DAI	4	4
single contusion	2	2
multiple contusions	4	5
intracerebral hematoma	2	1
acute subdural hematoma	7	10
acute extradural hematoma	2	1
traumatic SAH	2	4
traumatic IVH	1	—
depressed skull fracture	1	1

* There was no statistically significant difference between the groups. Abbreviations: CHI = closed head injury; DAI = diffuse axonal injury; IVH = intraventricular hemorrhage; SAH = subarachnoid hemorrhage.

† Pathological entity was classified according to admission head CT scan and clinical evaluation.

Data Collection

In each patient, we recorded the number of monitoring days, maximal daily ICP, mean maximal daily ICP, number of increased ICP episodes (≥ 20 mm Hg), minimal daily CPP, mean minimal daily CPP, and number of episodes of CPP less than 60 mm Hg during the entire monitoring period. In addition, in Group B patients, the mean daily brain tissue PO₂, number of episodes of compromised brain tissue PO₂ levels (PO₂ < 25 mm Hg), and number of ischemic brain tissue PO₂ levels (PO₂ < 15 mm Hg) were recorded during the monitoring period. Relevant variables and patient characteristics were then compared between the groups to determine whether there were any significant differences.

Patient Outcome

The mortality rate was recorded for patients who died during their hospital stay following injury. Among survivors, patient outcome at discharge was recorded as favorable if the patient was discharged to home or a rehabilitation center and as unfavorable if the patient required additional hospitalization or was transferred to a nursing home.

Statistical Analysis

Data are expressed as the mean \pm standard deviation of the mean or as the median when data were not normally distributed. Patient and physiological variables and outcome were compared using the Kruskal–Wallis nonparametric analysis of variance, Student t-test, chi-square approximate, or Mann–Whitney U-test, which were selected for their appropriateness to the measurement level and the distributional properties of the data, by using a commercially available statistical program (InStat for the Macintosh, version 2.03; GraphPad Software, San Diego, CA). Statistical significance was defined as a probability value less than 0.05.

TABLE 2

Monitored physiological variables among 53 patients who underwent ICP/ CPP-based therapy or combined ICP/ CPP and brain tissue PO₂-based therapy

Monitored Variable	Group A	Group B	p Value
ICP monitor (days per patient)	3.73 ± 3.89	5.76 ± 5.08	0.09
mean daily ICP (mm Hg)	15.22 ± 4.21	17.00 ± 7.36	0.34
mean max daily ICP (mm Hg)	21.52 ± 6.9	25.5 ± 9.5	0.16
no. of ICP episodes >20 mm Hg	5.30 ± 7.65	14.05 ± 22.85	0.43
mean daily CPP (mm Hg)	72.93 ± 8.76	72.90 ± 6.19	0.44
mean min daily CPP (mm Hg)	56.3 ± 9.6	57.7 ± 7.1	0.63
no. of CPP episodes <60 mm Hg	3.82 ± 4.97	8.00 ± 13.18	0.46

Results

Patient Characteristics

Fifty-three patients with a median ISS of 26 and an admission GCS score less than 8 were identified in the database. Twenty-five patients (17 male and eight female, with a mean age of 44 ± 14 years) underwent ICP and CPP treatments and composed Group A (Table 1). Twenty-eight patients (25 male and three female, with a mean age of 38 ± 18 years) underwent brain tissue PO₂-directed management, composing Group B. Age, mechanism of injury, and ISS (Group A, median ISS 26; Group B, median ISS 27) were not significantly different between the groups. In addition, the groups were similar when admission GCS score, pupillary response, pathological characteristics, and initial resuscitation were considered.

Physiological Variables

All monitors were placed within 6 hours of admission to the HUP. Data obtained from 4567 hours of continuous ICP monitoring in the ICU were analyzed. The mean duration of ICP monitoring, mean daily ICP, and mean daily CPP were similar in the two groups (Table 2). In addition, there was no significant difference in the mean maximal daily ICP, mean minimal daily CPP, and mean number of episodes of elevated ICP (ICP > 20 mm Hg) or reduced CPP (CPP < 60 mm Hg) among patients in both groups. Three patients who received PO₂-directed therapy experienced intractable intracranial hypertension; one was successfully treated using barbiturates, and two by decompressive hemicraniectomy. One patient in Group A required barbiturates to control elevated ICP.

Brain Tissue PO₂ Monitoring

Group B patients underwent direct brain tissue PO₂ monitoring and conventional ICP monitoring. Data from 2505 hours of continuous brain tissue PO₂ monitoring (Licox) were analyzed. The mean daily brain tissue PO₂ was 34.7 ± 12.3 mm Hg. One hundred forty-two episodes of compromised brain tissue PO₂ levels (PO₂ < 25 mm Hg) and 35 episodes of ischemic PO₂ levels (PO₂ < 15 mm Hg) were detected during the monitoring period (Table 2).

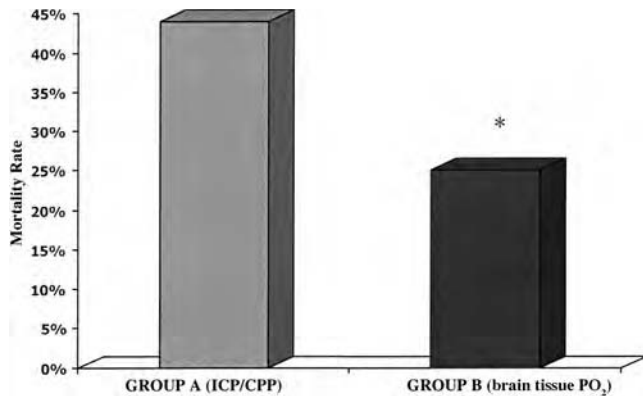


FIG. 1. Bar graph illustrating the mortality rates in patients who received traditional ICP/ CPP therapy (Group A, 25 patients) or combined ICP/ CPP and brain tissue PO₂ treatment (Group B, 28 patients). * $p < 0.05$.

Patient Outcome

To assess the impact of brain tissue PO₂-guided therapy, we determined whether there was improved survival and disposition at the time of hospital discharge. Eleven (44%) of the 25 patients who had undergone conventional ICP and CPP management died (Fig. 1). In contrast, brain tissue PO₂-directed treatment was associated with improved survival; that is, seven (25%) of these 28 patients died ($p < 0.05$). Furthermore, 17% of surviving patients (14 patients) who had undergone ICP/ CPP-guided management required additional hospitalization or nursing home placement (Fig. 2). None of the survivors (21 patients) in the brain tissue PO₂-guided group required nursing home placement; all were discharged to either home or a rehabilitation center.

Brain O₂ and Patient Outcome

Among patients who had undergone brain tissue PO₂-directed treatment, cerebral hypoxia episodes (< 15 mm Hg) were more frequent in those who died (1.23 ± 1) than in those who survived (0.34 ± 8 ; $p = 0.007$). In addition, the cumulative duration of compromised cerebral oxygenation (< 25 mm Hg) was significantly longer in those who died (364.1 ± 422.7 minutes) than in survivors (164.9 ± 362.9 minutes; $p = 0.04$).

Discussion

In this study consisting of 53 patients with severe TBI, we determined how a management strategy that included brain tissue PO₂ monitoring influenced the patient mortality rate at a Level I trauma center. Thus, we compared the outcomes among 28 patients who had been treated using ICP and brain tissue PO₂ monitors with those in 25 matched historical controls treated with an ICP monitor alone. Our results demonstrate that brain tissue PO₂ monitoring was associated with a significant reduction in patient deaths.

Methodological Limitations

Data in this study were collected prospectively in an observational database and have two main limitations. First, the small sample size—53—means that our results should

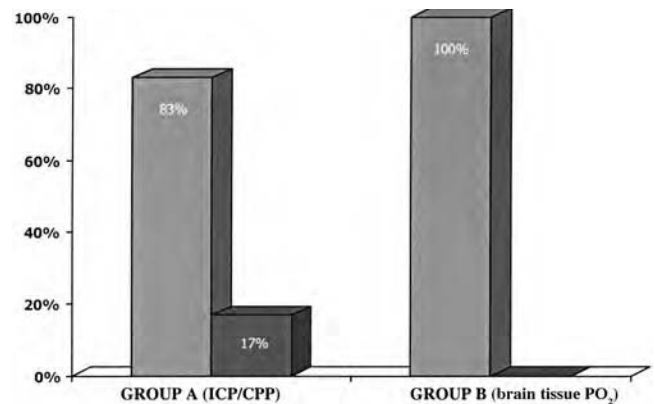


FIG. 2. Bar graph illustrating the discharge disposition among surviving patients who received traditional ICP/ CPP treatment (Group A, 14 patients) or combined ICP/ CPP and brain tissue PO₂ treatment (Group B, 21 patients). Discharge outcome was considered favorable if the patient was discharged to home or a rehabilitation center and unfavorable if the patient required additional hospitalization or was admitted to a nursing home. *Light gray bar* indicates favorable outcome; *dark gray bar* indicates an unfavorable outcome.

be regarded as preliminary but as nonetheless useful information in clinical practice or in designing further trials. Consider, for example, that prophylactic hyperventilation is not recommended in TBI management;³ however, this standard is based on a study that included 77 patients randomized to undergo either hyperventilation or normal ventilation.³⁴ Second, our study design is nonrandomized and represents historical controls. Note, however, that the same team of physicians and nurses in the same ICU provided patient care during the entire study period. In addition, treatment was not changed during the study period except for the introduction of brain tissue PO₂ monitoring and brain tissue PO₂-based therapy. We carefully matched patients for age, admission GCS score, ISS, and pathological entity. We believe therefore that our results indicate a beneficial effect. Ideally, a randomized clinical trial is necessary. Before such a trial, however, sufficient clinical data are needed to justify and plan for such an undertaking. It is interesting to note that the impact of ICP monitoring on patient outcome has yet to be directly evaluated, including in a randomized clinical trial.³

Monitoring ICP

Monitoring ICP has become routine in many neurointensive care units and is recommended in patients with severe TBI.^{3,5,36,37} Although the benefit of ICP monitoring has not been demonstrated in any clinical trial, the association between increased ICP and poor outcome has been well described.^{29,33,35,41} The primary reason to treat increased ICP (> 20 mm Hg) is to maintain adequate CPP and thus prevent cerebral ischemia or infarction, which adversely affects patient outcome. Note, however, that increased ICP is responsible for less than half the episodes of cerebral ischemia, and cerebral infarction can occur despite normal ICP and CPP.^{13,24,49} Furthermore, data from recent positron emission tomography studies demonstrate that in some patients with TBI, mechanisms other than simple perfusion-related ischemia may be responsible for cellular hypoxia in the brain.³¹

Reduction in mortality rate through brain tissue PO₂ management

Together these data indicate that although an ICP monitor is useful in treating TBI, monitoring other parameters also may be helpful.

Brain Tissue PO₂

Authors of several studies have posited that direct brain tissue PO₂ monitoring may be an ideal complement to ICP monitoring in TBI treatment.^{4,14,30,40,43,48,49} Brain O₂ values between 20 and 40 mm Hg are regarded as normal, whereas reductions to less than 10 to 15 mm Hg are associated with ischemia. In particular, a significant relationship between poor outcome and cerebral hypoxia has been consistently observed: the number, duration, and intensity of cerebral hypoxia episodes (brain tissue PO₂ < 15 mm Hg) and any brain tissue PO₂ values less than 6 mm Hg.^{11,25,40,46,47,49} are associated with worse patient outcome. Consistent with this result, prolonged systemic hypoxia following TBI also is associated with worse clinical outcomes.^{21,26} There are many factors that influence brain tissue PO₂, some of which are not detected by an ICP monitor. Furthermore, a direct relationship between CPP and brain O₂ is not observed in every patient, in large part because autoregulation frequently is disturbed.³⁹ Results from recent studies have also demonstrated that an increase in brain tissue PO₂ is associated with improved cerebral metabolism.^{32,45} Together these data indicate that it is reasonable to assume that the use of a brain tissue PO₂ monitor and efforts to increase brain O₂ delivery may improve TBI outcome.

Brain Tissue PO₂-Guided Therapy and Outcome

Results of this study demonstrate that brain tissue PO₂-guided treatment is associated with a significant reduction in death following TBI. There were several interesting observed differences, although not statistically significant, when patient clinical characteristics and monitored physiological variables were compared in the two groups. First, in the brain tissue PO₂ group there was a tendency for a longer course of monitoring. Second, in the brain tissue PO₂ group the mean ICP tended to be higher and patients tended to have more episodes of increased ICP. Although these differences were not significant, they may be important. As our experience with brain tissue PO₂ monitors has evolved we have become more tolerant of mild ICP elevation (20–30 mm Hg) in our patients provided that brain tissue PO₂ is not affected and that a head CT scan does not reveal a mass lesion. This may be of consequence because every ICP treatment has a potential deleterious side effect.^{7,8,18,28} We also noted more episodes of CPP less than 60 mm Hg in the brain tissue PO₂ group. Aggressive CPP management to avoid cerebral ischemia has recently come into question and may be deleterious in some patients, in part because the use of vasopressor therapy and large fluid administration to maintain CPP is associated with pulmonary complications.^{7,38} Thus, one must question strict adherence to a minimal CPP in all patients. Instead, we propose that brain tissue PO₂-guided management will determine the appropriate CPP for each individual and reduce potentially harmful side effects associated with therapies to maintain ICP and CPP. We believe that brain tissue PO₂-guided treatment will establish an appropriate regimen tailored to individual patient needs consistent with studies demonstrating

the marked heterogeneity in TBI pathological features and pathophysiology.²²

There is very limited research on how different monitoring techniques affect outcome following neurosurgical disorders. For example, although ICP monitoring is recommended in the TBI guidelines and has been in use since the 1960s, its benefits to patient outcomes have not been directly assessed in a clinical trial.³ There is some evidence from clinical series that measures in addition to ICP and CPP may be helpful. For example, in a clinical series including 353 patients, Cruz⁹ observed that patients treated with CPP and jugular bulb monitoring for cerebral O₂ extraction had better outcomes than those treated using CPP monitoring alone. Direct brain O₂ monitoring has become feasible in recent years. Its impact on patient outcome, like ICP monitoring, has been the subject of little direct study. Note, however, that Meixensberger and associates³⁰ recently evaluated its impact on outcome in 93 patients by using historical controls. All patients underwent brain tissue PO₂ monitoring, although in the first part of the study they received only ICP/ CPP-based therapy. Patients treated during the second part of the study with brain tissue PO₂ monitoring tended to have a better outcome. This difference was not statistically significant however.

There are several important differences between the study reported on by Meixensberger, et al.,³⁰ and ours. First, Meixensberger and associates attempted to maintain CPP above 70 mm Hg in their patients. Data from recent studies have indicated that strict adherence to this level may be deleterious in some patients and that a threshold of 60 mm Hg, as in our study, is instead the desired CPP. Second, the brain tissue PO₂ threshold for treatment was set at 10 mm Hg in their study. At that level, however, the brain is already severely hypoxic and ischemic. We set the brain tissue PO₂ treatment level at 25 mm Hg to prevent the development of critical hypoxia rather than needing to treat it once it had occurred. Third, Meixensberger and colleagues treated cerebral hypoxia only by increasing CPP. In the patients in our study we used a cause-specific management protocol, including the treatment of pulmonary abnormalities, administration of blood, treatment of fever, decompressive hemicraniectomy, and so forth, rather than treating ICP or CPP alone.⁴⁴ This tactic was important considering that in a recent clinical trial,³⁸ a CPP-based management strategy did not help patient outcome, in large part because the therapies used to increase CPP had an adverse affect on lung function.⁷ Consistent with this finding we recently observed that systemic oxygenation rather than CPP or ICP was associated with cerebral hypoxia in patients with multiple injuries.¹⁵

Conclusions

The concept of multimodality monitoring is not new. As brain tissue PO₂ monitoring gains increasing acceptance at head-injury centers and in neurointensive care units, it is critical to compare its use to ICP monitoring alone. In addition, as new information about current CPP management^{7,38} compels questions, we must identify better resuscitation end points. Brain tissue PO₂ monitoring may help in this process. Our results, although preliminary, are compelling and provide the first evidence that the use of multimodality monitoring with both an ICP and a brain tissue PO₂ monitor

as well as therapy directed at brain O₂ can be associated with a reduced patient mortality rate after severe TBI.

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