# Targeting Brain Tissue Oxygenation in Traumatic Brain Injury

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**The management of patients with traumatic brain injury has evolved in the last several years, due to the introduction of new, invasive monitoring devices. The ability to monitor parameters other than measurements related to pressures has generated substantial interest. Brain tissue oxygenation monitoring has been consistently shown to provide prognostic information, as indicated by poor prognosis associated with low brain tissue oxygen values. Furthermore, various physiologic manipulations, including increasing the $P_{aO_2}$, have been associated with an increase in brain tissue oxygenation. Whether brain-oxygenation-guided therapy results in improvement in outcomes is debatable. Retrospective studies suggest benefit, while prospective studies have shown a higher intensity of therapeutic interventions with no outcome differences. Data from high quality randomized trials are necessary to determine if brain-oxygenation-guided therapy is beneficial. An oxygen challenge (transient increase in $F_{IO_2}$ to 0.6 up to 1.0) to assess the responsiveness of the monitoring and ascertain the presence of technical malfunction is an accepted practice.** *Key words: oxygen; brain injury; trauma; brain; oxygenation.* [Respir Care 2013;58(1):162–169. © 2013 Daedalus Enterprises]

## Introduction

Traumatic brain injury (TBI) is a common cause of death and disability among adults, with a mortality as high as 40% within the first 48 hours, and a 20% rate of severe disability.[1] In survivors who reach the hospital, secondary ischemic injury to the brain is an important contributor to morbidity and mortality.[2] Intensive care for patients with TBI is focused on monitoring for and preventing secondary hypoxic injury. Intracranial pressure (ICP) monitoring

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Dr Treggiari presented a version of this paper at the 50th RESPIRATORY CARE Journal Conference, "Oxygen," held April 13–14, 2012, in San Francisco, California.

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DOI: 10.4187/respcare.01942

remains the standard monitor in neurocritical care, but additional monitors for brain tissue oxygenation ($P_{btO_2}$) are being increasingly utilized and investigated. The technical aspects of direct $P_{btO_2}$ monitoring, as well as a critical appraisal of the data regarding its use to guide treatment of patients with TBI, are the focus of this review.

## Pathophysiology of Secondary Brain Injury

Brain oxygenation is dependent on the content of oxygen in the arterial blood, cerebral blood flow, and metabolic activity of brain tissue; all 3 of these components can be altered in patients with TBI. A more recent concept of impaired brain function induced by hypoxia and ischemia is referred to as "spreading depression."[3,4] After an initial hyperemic response to injury, delays in energy-dependent recovery lead to hypoperfusion in tissue at risk of damage (an inverse hemodynamic response, or spreading ischemia). Impaired autoregulation of blood flow to the brain, hypotension, hypoxemia, elevated ICP, and increased metabolic requirements of injured brain tissue can jointly result in tissue ischemia and infarction.

Systemic hypoxemia was identified as a potential contributor to secondary brain injury approximately 30 years ago.[5] In 1993, Chesnut et al conducted a more detailed analysis of the effects of systemic hypoxia and hypotension on secondary brain injury, using data from the Traumatic Coma Data Bank.[2] These authors found that both hypoxia ($P_{aO_2} \leq 60$ mm Hg) and hypotension (single systolic blood pressure $< 90$ mm Hg) were independently associated with significant increases in morbidity and mortality from severe head injury. However, neither the Miller nor Chesnut studies adequately accounted for the effect of severity of illness and the cause of hypoxemia on mortality. Patients with TBI are at risk for hypoxemia of multiple etiologies, including coexisting polytrauma and neurogenic pulmonary edema. A number of pulmonary complications associated with prolonged ICU stay and mechanical ventilation, such as acute lung injury/ARDS, pneumonia, and volume overload, are common in patients with TBI, and may contribute to hypoxemia.[6,7] Furthermore, the development of pulmonary complications is associated with worse neurological outcome in patients with TBI.[8] Thus, the precise role that hypoxemia/systemic hypoxia plays in outcome after TBI is unclear, due to the confounding effect of associated illness and injury.

Patients with TBI also often receive vasopressors to maintain cerebral perfusion, and vasopressors have been shown to be associated with increased incidence of acute lung injury.[9] In at least one study, patients with a management protocol guided by $P_{btO_2}$ monitoring received significantly more vasopressors than those with ICP monitoring alone.[10] It is worth mentioning that the $P_{btO_2}$ monitor is not intended to be a monitor for hypoxemia or pulmonary complications of TBI.

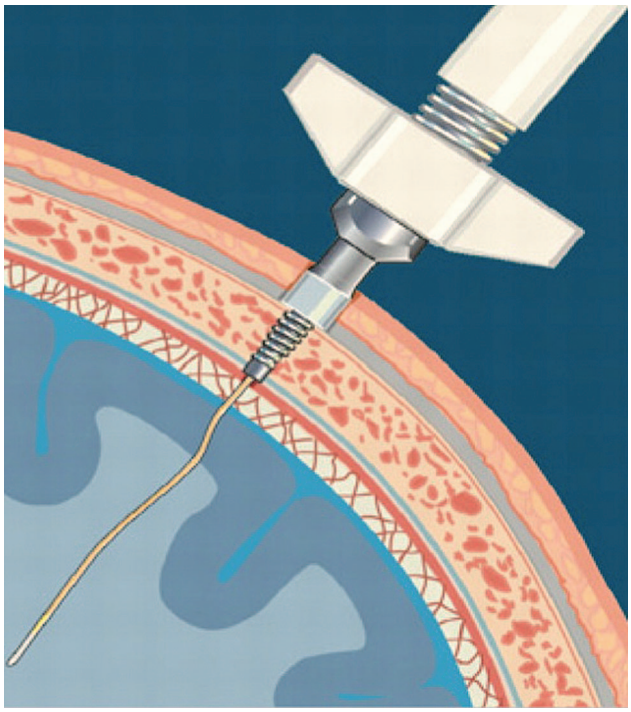

Figure. Coronal section illustrating the placement of the brain tissue oxygenation probe in the brain parenchyma. (Courtesy of Integra NeuroSciences.)

Detection of brain tissue at risk for secondary injury is a paramount goal of the care of patients with TBI. One of the most studied methods for reduction of secondary injury is direct monitoring of ICP.[11,12] Elevated ICP has been associated with poor outcome, and medical and surgical interventions to reduce ICP are associated with improvement in vital outcomes.[13,14] However, ischemic injury can occur even in the absence of increased ICP, reflecting the flaw in the assumption that cerebral perfusion pressure is an adequate surrogate for cerebral blood flow.[15–17] For this reason, several adjunct monitoring modalities have been developed to measure cerebral oxygenation, both directly and indirectly. One candidate for detection of ischemic secondary injury is the direct brain tissue oxygen monitor, which was recently included into the guidelines for management of severe TBI.[18]

## The Brain Tissue Oxygen Monitor

### Technical Aspects

The brain tissue oxygen monitor is a thin, metallic electrode that measures dissolved oxygen in a small area of brain tissue (Figure). Until recently, two commercial and technologically different probes for $P_{btO_2}$ monitoring have been available in the United States: one as a standalone

tissue oxygenation sensor, recently upgraded to include ICP and brain temperature monitoring (Licox Brain Tissue Oxygen Monitoring, Integra LifeSciences, Plainsboro, New Jersey), and the other combined with an ICP monitor, temperature, and pH/$P_{CO_2}$ sensor (Neurotrend, Diametrics Medical, High Wycombe, United Kingdom), which is no longer manufactured. The metallic tip of the Licox $P_{btO_2}$ monitor is a combination of 2 polarographic Clarke type electrodes covered in a semipermeable membrane at the tip of a flexible micro-catheter. In the presence of dissolved oxygen, one electrode reduces oxygen to water and generates an electrical difference, which is interpreted by the monitor as a particular value for oxygenation. While this is a quite precise and accurate way to measure dissolved oxygen, it is a highly localized measurement, with a sampling area of 7.1–15 $mm^2$.[19]

## What $P_{btO_2}$ Measures

What $P_{btO_2}$ represents in terms of the physiology of oxygen supply/demand in the brain remains under discussion. Most simply stated, the monitor measures free, dissolved oxygen. However, total oxygen delivery and cerebral oxygen metabolism are related to the oxygen *content* of blood, and only a small portion of blood oxygen content is dissolved:

$$C_{aO_2} = (\text{hemoglobin} \times 1.36 \times S_{aO_2}) + (0.0031 \times P_{aO_2})$$

where $C_{aO_2}$ is the arterial oxygen content of the blood, and $S_{aO_2}$ is the arterial oxygen saturation.

Rosenthal et al recently evaluated the determinants of $P_{btO_2}$ in patients with severe TBI.[20] Patients were given an oxygen challenge with $F_{IO_2}$ of 1.0 or an increase in mean arterial pressure, and changes in $P_{btO_2}$ in response to these 2 interventions were measured. $F_{IO_2}$ challenge linearly increased both the $P_{aO_2}$ and the $P_{btO_2}$, but had no effect on the cerebral metabolic rate for oxygen or oxygen delivery. Likewise, an increase in mean arterial pressure resulted in a small increase in cerebral blood flow and $P_{btO_2}$, but there was no change in the cerebral metabolic rate for oxygen. These observations suggest that the $P_{btO_2}$ is a measure primarily reflecting the oxygen dissolved in the blood and diffused in the cerebrospinal fluid and interstitial space, and not a measure of oxygen metabolism or delivery to the tissues. Gupta et al validated the measurements of the $P_{btO_2}$ sensor (Neurotrend) versus positron emission tomography in 16 patients, using $P_{aCO_2}$ reactivity.[21] There was no correlation between end capillary $O_2$ tension derived from $O_2$ extraction fraction and $P_{btO_2}$ values; however, $P_{btO_2}$ changes in response to $P_{aCO_2}$ reactivity were highly correlated, suggesting that, while absolute values may not substitute for direct measures of oxygenation, change may be helpful in assessing responsiveness to therapeutic interventions. These observations call into question whether intervening on low $P_{btO_2}$ values can affect outcome. Some argument exists that higher partial pressures of oxygen could increase oxygen diffusion into tissues and overcome tissue barriers to diffusion, even without substantial changes in oxygen delivery.[22] Hyperoxia remains of unclear benefit, however, and, in fact, experimentally may have deleterious effects on metabolically fragile areas of ischemic brain exposed to reperfusion-driven oxidative stress.[23]

## Appropriate Placement of the Monitor

The monitor can be placed through the same burr hole as an ICP monitor (single lumen), and a new double catheter is now available to allow measurement of ICP, $P_{btO_2}$, and temperature simultaneously. As opposed to ICP measurement, the location of placement critically affects the values of $P_{btO_2}$ measured. Placement into an area of damaged brain, compared to placement into a relatively normal area, will result in vastly different data that fail to reflect global dissolved oxygen in either case.[24] Placement on the more injured side of the brain will reflect the area at most risk for secondary injury. Placement on the less injured side could be extrapolated as a more global assessment of oxygenation, but it may not capture the environment of the tissue at highest risk for injury.[25] Therapies to intervene on low $P_{btO_2}$ values may also preferentially affect the uninjured brain tissue being monitored, and imply a false therapeutic benefit on penumbral brain issue.[26] This highly localized view of the brain, along with the inability to provide information on oxygen consumption, is a major limitation of the monitor. Figure 1 illustrates the positioning of the $P_{btO_2}$ monitoring probe in the brain parenchyma.

## Complications

Complications associated with the $P_{btO_2}$ monitor have been reported but are infrequent. It can be inserted through the same burr hole as an ICP monitor, so poses little additional risk. One of the first reports of experience with use of the $P_{btO_2}$ monitor reported a 1.7% rate of iatrogenic hematoma, which is similar to that of ICP monitoring. No reports of infection were made in that series, but there was a high rate of technical malfunction of the monitor (13.6%) that necessitated replacement.[27] After insertion there is a period of a few hours where the data collected by the monitor are inaccurate, due to local trauma associated with its insertion.

## Association Between Brain Tissue Hypoxia and Outcome

Irrespective of the technical limitations of the monitor, the association between brain tissue hypoxia and poor outcome is well established. Both the depth and duration of episodes of brain tissue hypoxia have been associated with

increased mortality and worse long-term neurological outcome in TBI and subarachnoid hemorrhage patients.[28] Normal values for $P_{btO_2}$ in animal studies have been reported as between 25–30 mm Hg,[29] and thresholds for intervention in human patients with TBI have been established based on several observational studies.[18] Higher mortality has been described with increasing duration of $P_{btO_2}$ values below 15 mm Hg, and instances of any duration of $P_{btO_2}$ below 6 mm Hg.[30] In 1998, Bardt et al found that $P_{btO_2}$ values $<$ 10 mm Hg for $>$ 30 min were associated with 56% mortality, compared to 9% in those without. The likelihood of a good neurological outcome was similarly reduced to 22%, compared with 73% in patients without prolonged brain tissue hypoxia.[31] One recent review of the literature found a 4-fold increase in the odds of death or disability at 6 months in patients with $P_{btO_2}$ $<$ 10 mm Hg at any time.[32] It is therefore well established that low $P_{btO_2}$ is a strong indicator of poor prognosis. Given the strong association between low $P_{btO_2}$ and outcome, it is logical to question whether correcting poor values with aggressive therapeutic interventions alters the course of brain ischemia and leads to better outcomes, or whether low $P_{btO_2}$ is simply a marker of higher disease severity.

## Targeting Brain Tissue Oxygenation

The general strategy for correction of hypoxic $P_{btO_2}$ relies on correcting the underlying cause. Patients with low $P_{btO_2}$ values as a result of global hypoxemia should receive interventions to correct hypoxemia. Airway recruitment, increased PEEP, and increased $F_{IO_2}$ can be effective, depending on the etiology of hypoxemia, but these interventions are potentially associated with increased incidence of ventilator-induced lung injury,[33] and should be used only to correct hypoxemia, generally irrespective of the $P_{btO_2}$ value.

Medical interventions to improve $P_{btO_2}$ in the absence of hypoxemia are parallel to those used to reduce ICP. The threshold for treatment of brain tissue hypoxia varies between institutions, but generally treatment becomes indicated for $P_{btO_2}$ values $<$ 20 mm Hg. A tiered approach with escalating aggressive therapy is usually implemented. Initial relatively benign interventions include adjustment of the head of bed to above 30°,[34,35] and temperature management to below 37.5°C.[36]

Prior to initiating more invasive treatment, the first reaction to brain tissue hypoxia is to perform a brief $F_{IO_2}$ 1.0 challenge to assess the reliability of the $P_{btO_2}$ values.[21] $P_{btO_2}$ should rise in tandem with the $P_{aO_2}$. The therapeutic benefit of hyperoxia is disputed, however. In theory, any benefit of increasing the dissolved oxygen is marginal, since dissolved oxygen is only 2–3% of blood oxygen content, at maximum. However, some data do suggest a metabolic benefit to hyperoxic therapy to treat low $P_{btO_2}$. Recent work has shown that, after an $F_{IO_2}$ challenge, brain lactate and glutamate, measured by a microdialysis catheter, decreased, and glucose increased, at comparable levels of cerebral perfusion.[37] It should be noted that these observations were obtained in patients with progressing injuries, without steady state baseline measurements, and receiving concomitant treatments. While brain metabolic biomarkers appeared to be improved, 3- and 6-month outcomes were not different. Similar work was previously published suggesting a reduction in lactate production in a cohort treated with increased $F_{IO_2}$; however, baseline measures were unstable, making it difficult to interpret the effect attributable to the intervention above and beyond the natural course of the brain metabolic biomarkers.[38]

Interestingly, observational studies have shown poor correlation between elevated ICP and $P_{btO_2}$, as well as lack of correlation with $P_{aCO_2}$ and hemoglobin level.[39] However, transfusion of packed red blood cells to a target hemoglobin of $\geq$ 10 g/dL may be more effective to increase the oxygen-carrying capacity of blood,[40] than increasing $F_{IO_2}$. Likewise, cerebral ischemia may occur in the presence of normal ICP, due to multiple intervening mechanisms not captured by global measurements such as microvascular abnormalities, impaired autoregulation, or localized edema. Taken together, these observations suggest that, rather than relying on the absolute $P_{btO_2}$ numbers, trending the change in $P_{btO_2}$ values over time might be a more valuable tool to evaluate the response to therapy.

Patients with concomitant intracranial hypertension generally receive interventions primarily directed at raising cerebral perfusion pressure, either via increasing mean arterial pressure or decreasing ICP.[11,41] Aggressive treatments to improve cerebral perfusion pressure are not without consequence,[42] and many of the same treatments are indicated for the management of brain tissue hypoxia. The use of vasopressors to raise cerebral perfusion pressure is a risk factor for pulmonary complications,[9] which in turn have been associated with worse neurological outcome following TBI.[8] The use of heavy sedation or induced coma to decrease ICP could also result in increased duration of mechanical ventilation and length of hospital stay.[43]

## Outcome of Management Guided by Brain Tissue Oxygenation

Several observational studies have been published comparing $P_{btO_2}$-guided management with ICP-guided management alone, and are summarized in the Table.[10,44-49]

Meixensberger et al[44] first observed that, while $P_{btO_2}$-guided management of cerebral perfusion was associated with relatively fewer episodes of cerebral hypoxia, there

Table. Characteristics of Studies Comparing Outcomes of Patients Monitored With Intracranial Pressure Alone or Intracranial Pressure and Partial Brain Tissue Oxygen Pressure

| First Author | Group | *n* | $P_{btO_2}$ Treatment Threshold (mm Hg) | Control Group | End Points | Admission Glasgow Coma Score | Injury Severity Score | Outcome (%) | Mortality (%) |
|---|---|---|---|---|---|---|---|---|---|
| Meixensberger[44] | ICP | 40 | | Historical | Glasgow outcome score Good outcome | 6 (4–7) | NR | 54* | NR |
| | $P_{btO_2}$ | 53 | < 10 | | | 6 (4–7) | NR | 65* | NR |
| Steifel[45] | ICP | 25 | | Historical† | Discharge Rehabilitation facility/home versus skilled nursing facility | < 8 | 26 (17–45) | 83* | 44 |
| | $P_{btO_2}$ | 28 | < 25 | | | < 8 | 27 (17–50) | 100* | 25‡ |
| Adamides[46] | ICP | 18 | | Concurrent | Mean Glasgow outcome score | 5.8 ± 0.5 | 34 ± 3 | 2.6§ | 44 |
| | $P_{btO_2}$ | 18 | < 15 | | | 6.0 ± 0.7 | 33 ± 3 | 3.4§ | 22 |
| Martini[10] | ICP | 506 | | Concurrent | Mean Functional Independence Score | 5.6 ± 2.3 | 35 ± 13 | 8.6 ± 3§ | 23 |
| | $P_{btO_2}$ | 123 | < 20 | | | 5.1 ± 2.2‡ | 40 ± 13‡ | 7.6 ± 3‡§ | 29 |
| McCarthy[47] | ICP | 64 | | Historical | Glasgow outcome score Good outcome | 4.6 ± 2.1 | 26 ± 8 | 61* | 36 |
| | $P_{btO_2}$ | 81 | < 20 | | | 4.0 ± 1.8 | 27 ± 10 | 79* | 31 |
| Narotam[48] | ICP | 41 | | Historical | Mean Glasgow outcome score | 7.3 ± 4.8 | 27 ± 9 | 2.7 ± 1.7§ | 42 |
| | $P_{btO_2}$ | 139 | < 20 | | | 5.9 ± 3.7‡ | 32 ± 13‡ | 3.6 ± 1.8‡§ | 26 |
| Spiotta[49] | ICP | 53 | | Historical | Glasgow outcome score Good outcome | GCS: 3 77% | 35 ± 14 | 40* | 45 |
| | $P_{btO_2}$ | 70 | < 20 | | | GCS: 3 67% | 35 ± 12 | 64* | 26 |

* Represents percentage of patients whose outcome was scored as "good."
† Controls matched to cases for Glasgow Coma Score (GCS).
‡ Significant compared to control group.
§ Mean outcome score.
$P_{btO_2}$ = partial pressure of brain tissue oxygen
ICP = intracranial pressure
NR = not reported

was no difference in neurological outcome at 6 months, using the Glasgow Outcome Scale, which is a 5-level scale in which 1 is death, 2 is a vegetative state, 3 is severe disability, 4 is moderate disability, and 5 is good functional recovery.[50] A much improved version, the Glasgow Outcome Scale-Extended, is now available.[51] Meixensberger et al[44] used a historical group as controls, and the patients in the control group had $P_{btO_2}$ monitors in place that were not used to guide management. Interestingly, in both groups, there was a U-shaped distribution of episodes of brain tissue hypoxia: in the first day after injury, and peaking again on days 7–10. The early episodes of brain tissue hypoxia appeared to be less modifiable by $P_{btO_2}$-guided therapy whereas later episodes of hypoxia were relatively more common in the group without $P_{btO_2}$-guided management. Perhaps this suggests that there are multiple mechanisms underlying brain tissue hypoxia and those that occur early after injury are less modifiable but more highly predictive of outcome. The outcomes measured were not adjusted for potential confounders, and it is unknown if the results would have been different after accounting for differences in patient characteristics.[44]

In a prospective, observational study, Narotam et al[48] compared an ICP-guided protocol with one supplemented with $P_{btO_2}$ monitoring in 139 patients with TBI and major trauma. The investigators found that patients monitored with both ICP and $P_{btO_2}$ monitoring had almost twice the odds of a good neurological outcome, as defined by 6-month Glasgow Outcome Scale scores. They also observed a roughly 15% absolute reduction in mortality, when compared to historical controls. The patients with $P_{btO_2}$ monitoring had significantly worse admission Glasgow Coma Scale scores, and worse injury severity scores, but other differences between the groups, such as the mechanism of injury and the intracranial pathology, were not compared between the groups. Also, the outcome measures were not adjusted to take into account differences in confounding factors, though these would likely favor an additional benefit for $P_{btO_2}$ monitoring, as this group had worse prognosis at admission. This study does confirm that brain tissue

hypoxia is associated with increased odds of death and poor functional outcome, especially when $P_{btO_2}$ is low in association with refractory elevated ICP over a long period of time.[48]

McCarthy et al[47] compared 48 patients with ICP monitoring to 63 patients with multimodal $P_{btO_2}$ monitoring, and found a 70% increase in the odds of a good neurological outcome at 3 months with multimodal monitoring. Spiotta et al[49] compared similar numbers of patients, and reported a nearly 3-fold increase in the odds of a favorable outcome in patients with multimodal monitoring, as well as significantly improved mortality.

One recent meta-analysis pooled the results of these studies[10,45–48] and found that $P_{btO_2}$-guided management nearly doubled the odds of a favorable neurological outcome.[52] All of the included studies were retrospective, utilized historical controls, and measured outcome based on the Glasgow Outcome Scale. Three studies were not included in the meta-analysis by Nangunoori et al,[52] due to the lack of reporting of the Glasgow Outcome Scale data.

Adamides et al[46] conducted a small, retrospective analysis of $P_{btO_2}$-guided management compared to both historical and concurrent controls. The authors noted trends toward better outcome and improved mortality in patients with $P_{btO_2}$-guided management, but the number of patients included in the study was very small, and none of their differences in outcome measures were statistically significant.

In a study of 53 patients, Stiefel et al[45] observed that patients who received $P_{btO_2}$-guided interventions had decreased mortality (25% vs 44%), when compared to historical, case-matched controls monitored with ICP only. Data regarding Glasgow Coma Scale scores at admission are not detailed, but the authors report that the entire population had an admission Glasgow Coma Scale $< 8$. They also did not specifically measure outcomes other than mortality, but report that 100% of patients who received $P_{btO_2}$ monitoring were discharged to home or rehabilitation centers, compared to 87% of patients with ICP monitoring.[45]

Only one study has shown no benefit to $P_{btO_2}$-guided therapy for patients with severe TBI, and was conducted by the authors of this review.[10] While we demonstrated differences in the ICU course of patients with brain tissue oxygen monitoring, most notably increased resource utilization, longer mechanical ventilation, and increased costs, we did not find a reduction in hospital mortality or functional outcome in patients with severe TBI who were managed with $P_{btO_2}$ monitoring. We reported a mortality of 29% in patients with multimodal monitoring, compared with 23% for ICP monitoring alone, and significantly worse functional outcome in patients with $P_{btO_2}$ monitoring.

The major limitation of this study was the utilization of a concurrent control group. The $P_{btO_2}$-monitored patients were selected at the discretion of the admitting neurosurgeon, without specific guidelines for insertion, which resulted in the group of patients receiving $P_{btO_2}$ monitoring having significantly worse neurologic injury at presentation, and a worse prognosis. While statistical adjustments were made for the imbalances in baseline characteristics predictive of prognosis, it is likely that residual confounding was present. What we did emphasize, however, is that many more of the patients in the $P_{btO_2}$ group received therapeutic interventions to manage hypoxic $P_{btO_2}$ values, each with possible adverse systemic consequences, and at significantly increased institutional cost, without a clear benefit on outcome.[10]

An important issue with several of the studies described above is the utilization of historical controls. Steifel et al[45] and Narotam et al[48] report mortality of 44% and 42%, respectively, in the group receiving ICP monitoring alone, which is on average high, when compared to other United States trauma centers, irrespective to the monitoring modality used. Only the mortality of their $P_{btO_2}$-monitored group (25% and 26%, respectively) were similar to that seen in TBI patients in United States trauma centers in general.[1,53] This suggests that differences in mortality could have been the result of temporal trends rather than the actual effect of therapies used. The treatment protocols employed by each study to treat low $P_{btO_2}$ were also varied, making it difficult to ascertain which components of $P_{btO_2}$-guided therapy, if any, were beneficial. Given these limitations, the need for further study of $P_{btO_2}$-guided management is clear.

An ongoing phase II multicenter trial is currently recruiting TBI patients, with an enrollment goal of 132 subjects. Patients are randomized to ICP-guided monitoring or ICP- and $P_{btO_2}$-guided monitoring, using a tiered approach to escalate therapy. The results of this trial will provide important data to reconcile the findings of the observational studies and likely preliminary estimates for the planning of a larger phase III trial.

## Summary

The avoidance of secondary injury to the brain following TBI is an important focus of neurocritical care. Brain tissue hypoxia measured by a direct intraparenchymal electrode is associated with poor vital and neurological outcome. While $P_{btO_2}$ is a modifiable variable in the post-injury period, and although there is a suggestion of improved outcomes among patients managed with $P_{btO_2}$-guided therapy, whether or not this translates into an improvement in clinical outcomes overall remains to be confirmed. The observational studies on targeting brain tissue oxygenation are difficult to compare, especially given the variation of the treatment protocols used, as these are the true modifiers of outcome. At present it is reasonable to consider the $P_{btO_2}$ monitor as a valuable tool to evaluate the response to

brain resuscitation interventions; however, implementing therapies to target a specific $P_{btO_2}$ value seems premature, based on the available literature. A randomized trial is needed to evaluate the efficacy of a brain tissue hypoxia directed management protocol, and until then wide utilization of $P_{btO_2}$ monitoring-based therapy cannot be recommended.

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## Discussion

**Kevin Ward:** Do you currently do microdialysis at the same time?

**Treggiari:** No, we don't use this technology in clinical practice.

**Kevin Ward:** I ask because I'm curious about the data you showed on lactate and glucose but not pyruvate. You would really need lactate and pyruvate to understand the redox reaction, because the brain can use lactate as a fuel, so you never know if it's coming or going. Are there plans to look at the microdiasylate for these entities?

**Treggiari:** Our neurosurgeons have been considering this for several years, but outside the investigational interest there are no established clinical guidelines or convincing data supporting improved outcomes with this monitoring modality, so we are not using it in clinical practice.

**MacIntyre:** I deal with patients who do not have neurological issues such as ICP problems or TBI. But I do have people who are very hypoxemic and are on lots and lots of respiratory support: high $F_{IO_2}$ and high ventilator pressures. I raise the possibility of maybe using this kind of technology in non-brain-injured patients to guide things like ventilator therapy. Kevin raised the point that maybe splanchnic monitoring may be better. Are there studies on this kind of technology in non-brain injured patients?

**Treggiari:** To my knowledge there are no studies of monitoring brain oxygenation in the absence of any detectable brain injury. That could be an interesting research area. I would

expect that, as long as the brain has normal auto-regulation, it would be unlikely to observe responses outside those predicable based on neurophysiology. In older literature there was concern about adverse neurological outcomes in patients rapidly exposed to permissive hypercapnia. To my knowledge there is not a clear attributable effect of hypoxemia or hypercapnia per se on neurocognitive function. It's certainly a possibility, but it's difficult to tease out, due to the multitude of factors intervening during critical illness.

**Kallet:** I was interested but not quite sure I followed the part about brain metabolism. I got the impression from that study[1] that the patients weren't really stable at baseline—there was some question about that. Is that true?

**Treggiari:** Correct: the baseline was not steady, at least in the representative patient represented in that figure.

**Kallet:** Secondly, the lactate was normal and went down, so you'd assume the metabolism had dropped. Did the glucose go up?

**Treggiari:** The glucose stayed the same and didn't increase, so it is difficult to interpret those data.

**Kallet:** What I'm driving at relates to what is known about the effects of hyperoxia in the lungs. Cells with higher metabolic rates appear to be particularly vulnerable to $O_2$ toxicity. For instance, the pulmonary capillary endothelium is the primary site of hyperoxia-induced lung injury. Andrea Harabin did a study of hyperoxia years ago, showing that, over the course of 4 days, pulmonary endothelial damage caused cellular metabolism to drop by 50%.[2] So it wouldn't strike me as extraordinary that even a few hours of hyperoxia in the brain might interfere with metabolism. Because hyperoxia interferes with enzymes—maybe not to a toxic level where necrosis or apoptosis would be evident, but it seems reasonable that several hours of hyperoxia could disrupt normal enzymes function.

**Treggiari:** One of the therapeutic goals is to shift brain metabolism from anaerobic to aerobic metabolism. In the study of induced hyperoxemia it is unclear if hyperoxemia affords an increase in aerobic metabolism versus a shift or reduction in metabolic activity.

**Kallet:** I don't think the interest in neurotrauma and neurologic research has been on the effects of hyperoxia. I think most of the concern is hypoxemia, so I'm not sure there are any animal data on hyperoxia and brain injury.

**Treggiari:** Some experimental data suggest that hyperoxia could be deleterious during reperfusion injury in the ischemic brain.[3] Hyperoxia could increase the availability of free oxygen radicals and increase oxidative stress, which we would try to avoid.

**Criner:** How much is known about regional $P_{btO_2}$ variation in the normal brain?

**Treggiari:** We actually know more about the abnormal brain. There is a lot of variability in the contused, damaged brain, but I am not aware of data on physiologic variations in the normal brain, except for the validation of normal values. In patients with brain injury intensively monitored with 2 $P_{btO_2}$ probes on each side, we frequently observe that the values are substantially different.

**Criner:** Do you think that regional variation may contribute to the lack of association?

**Treggiari:** It could be due to regional variation, but it could also be just technical malfunction or an issue of positioning. These are limitations related to what measurement the monitoring device is really capturing.

**Criner:** For the study you did, do you have any sense as to how different the $P_{btO_2}$ was in the patient you were monitoring for systemic manifestations of improved outcomes like systemic $O_2$ transport or global $O_2$, as opposed to regional?

**Treggiari:** Yes, we have a relatively good idea. These are, in general, young and otherwise previously healthy patients with isolated traumatic brain injury, so overall we expect that the global $O_2$ transport to be within normal physiologic values. This also means that, unlike patients with multiple trauma, there is less contribution to the inflammatory response other than the brain dysfunction.

**Criner:** In your study, could you see whether there was any association between an upper limit or the relationship between $P_{btO_2}$ and outcome, in the sense of whether it's a U shape relationship or a direct linear correlation?

**Treggiari:** That's an interesting point, and we have not looked at the shape of the relationship. However, in these patients we are actively treating the $P_{btO_2}$, and not just observing its natural course. The data would need to be interpreted in the context of someone who's actively trying to resuscitate these patients and normalize their $P_{btO_2}$ values.

**Claure:** Did you consider the changes in brain metabolism with hypothermia? And in the case of brain death, what readings would you obtain? Do you see any advantage to non-invasive near-infrared monitoring of the brain in neonates?

**Treggiari:** In adults the thickness of the skull makes it difficult for the energy to penetrate to sufficient depth,

so the near-infrared technology is unreliable. In neonates, who have a thinner, less calcified skull, this technology might provide better and more reliable information. The question of brain death is interesting. A recent study in a pig model of brain death showed a drop in $P_{btO_2}$ below 10 with increasing intracranial volume, while the lactate/pyruvate ratio continued to increase.[4]

**Pierson:*** I applaud your caution and objectivity in evaluating this new technology—especially coming, as you do, from an institution where there is strong advocacy and involvement in its use. It emphasizes to me the distinction between how we develop and learn about technology in health care, as compared to the situation with pharmaceutical agents. For a new pharmaceutical agent, it gets developed, it then is rigorously studied, and only after a study in the population for whom it is intended does it then get licensed, introduced, and finally widely used. Technology, particularly in the critical care unit, gets developed with typically a strong theoretical rationale, and is then directly introduced into clinical practice and often very widely adopted and used, and only finally some time later does it get properly studied.

I'm afraid I was reminded of the Swan-Ganz catheter as you were talking, as a technology with a compelling rationale that in the hands of the people advocating for it seemed to be great stuff. As you've pointed out, the device you're describing is just now entering that final phase of a randomized controlled trial, so we'll see how that turns out. But I think the history of critical care, which applies to a certain degree to $O_2$ in all contexts, but especially in critical care, is of the introduction of some exciting new thing, which quickly gets widely used, and only later gets studied, and many times found not to have the properties its advocates claimed.

**Treggiari:** I completely agree. The introduction of this monitoring device in clinical practice reminds me very much of the history of the pulmonary artery catheter. It's interesting that it's really about what we do with the information acquired from the monitor, and not just the monitoring itself. From the FDA's perspective, these devices are not "approved," they're "cleared" for use, which somehow has a less rigorous requirement for investigation than a product that requires approval.

**Kevin Ward:** One of the big issues for me (and perhaps for the readers), based on your overview, is not the concept of monitoring, but the concept that increasing your $F_{IO_2}$ to increase your $P_{aO_2}$ is therapeutic at the tissue level. If we look at the whole equation for $O_2$ delivery, we would say that getting your $P_{O_2}$ above 100 mm Hg wouldn't really provide any extra oomph or fuel in terms of $O_2$ for your tissue. One camp—which our neurosurgeons are definitely in—believes that an increase in $F_{IO_2}$ is therapeutic for TBI: that's the Richmond camp. Others feel differently about this.

But I think what's really the intriguing thing is that this little bit of extra $P_{O_2}$ that can be delivered to the tissue by increasing $F_{IO_2}$ is therapeutic. The fact that you have the ability to monitor that could be gratifying, but the key is not whether or not the monitor makes a difference, but whether or not increasing the $P_{O_2}$ by 10 mm Hg in the brain by dialing up the $F_{IO_2}$ can save brain cells.

**Treggiari:** I'm skeptical about that idea of increasing the $F_{IO_2}$. We allow this to happen for a short time, to evaluate the responsiveness of the measurements to changing conditions. Other than that, I believe that adjusting the $F_{IO_2}$ just to make the number look better does not provide a real benefit to the patient. As I said, the metabolic data are really not convincing, and it is uncertain that by delivering the extra $O_2$ we are making a difference.

**Branson:** When this first came about at my institution, I would find patients with isolated head injury on APRV [airway pressure release ventilation] and 100% $O_2$. And there seemed to be competing interests for increasing the brain tissue $P_{O_2}$ and really tearing up the lungs with large tidal volumes and higher airway pressures. This $F_{IO_2}$ challenge is clearly different in the TBI patient with a pulmonary contusion and a liver injury than it is in a patient with an isolated blunt trauma to the head and no other injury. What do you think is the primary lung pathology in patients with isolated head injury? Why are they hypoxemic? We tend to treat it like it's ARDS, but sometimes I think it's just ventilation-perfusion mismatch, often related to the perfusion, not the ventilation.

**Treggiari:** The criteria compatible with a diagnosis of neurogenic pulmonary edema are actually quite rarely met. We estimate it to be no more than 6%. Neurogenic pulmonary edema is typically seen in patients with extensive and severe TBI: it is not characteristic of patients with mild brain injury. The mechanisms leading to neurogenic pulmonary edema are multifactorial, but there is evidence of an inflammatory process leading to endothelial injury and impaired capillary permeability. Therefore it's not a simple hydrostatic problem related to cardiac dysfunction leading to cardiogenic edema. Because it's an inflammatory process, it is unlikely to respond to diuretics. The fluid in the alveoli is albumin and protein rich, so the treatment approach should be similar to that for ARDS.

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**Kallet:** A paper in *Critical Care Medicine* described the incidence of ALI [acute lung injury] and ARDS in neurological illness, which was about a third of these patients.[5] Basically they found that pneumonia was the leading cause of ALI, and it was associated with the loss of cough and gag reflex from impaired lower brain stem function. So a lot of these patients tend to have aspirated, and it's not usually picked up that they meet the ALI or ARDS criteria.

**Treggiari:** We published a study some years ago, with Gordon Rubenfeld, on the incremental mortality associated with developing ARDS in patients with trauma, including brain injury.[6] After accounting for severity of injury and some other potential confounders, we did not observe attributable incremental mortality in these trauma patients.

**Branson:** I've been impressed that in some of these cases the neurosurgery guys will call me and tell me they're having trouble with increasing $P_{aO_2}$—and I'm not advocating giving it to everybody, but 1-10 ppm of inhaled nitric oxide in head injury patients will sometimes triple their $P_{aO_2}$. I think aerosolized prostacyclin might do the same thing. But the issue is that there seems to be something unique about that group of patients, that ventilation-perfusion matching is different and can be modified by an inhaled vasodilator. Have you had that experience?

**Treggiari:** I haven't looked specifically at the response in TBI, but I did some work on how we can predict the response to inhaled nitric oxide in patients with ARDS. We did a study on cardiac function, and particularly the stretch of cardiac chambers, using ANP [atrial natriuretic peptide] and BNP [brain natriuretic peptide] as biomarkers,[7] and the indexes of cardiac stretch, as measured by elevated BNP/ANP, were predictive of the response to inhaled nitric oxide. It is possible that TBI patients with acute myocardial dysfunction (neurogenic stunned myocardium), and maybe acute pulmonary hypertension, may respond better to inhaled nitric oxide. However, this is very speculative at this point.

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