The role of lung function in brain tissue oxygenation following traumatic brain injury

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Object. Previous studies have demonstrated that periods of low brain tissue oxygen tension (PbtO₂) are associated with poor outcome after head trauma but have primarily focused on cerebral and hemodynamic factors as causes of low PbtO₂. The purpose of this study was to investigate the influence of lung function on PbtO₂ with an oxygen challenge (increase in fraction of inspired oxygen [FiO₂] concentration to 1.0).

Methods. This prospective observational cohort study was performed in the neurointensive care unit of the Level 1 trauma center at San Francisco General Hospital. Thirty-seven patients with severe traumatic brain injury (TBI) undergoing brain tissue oxygen monitoring as part of regular care underwent an oxygen challenge, consisting of an increase in FiO₂ concentration from baseline to 1.0 for 20 minutes. Partial pressure of arterial oxygen (PaO₂) and the ratio of PaO₂ to FiO₂ (the PF ratio) were determined before and after oxygen challenge.

Results. Patients with higher PF ratios achieved greater PbtO₂ during oxygen challenge than those with a low PF ratio because they achieved a higher PaO₂ after an oxygen challenge. Lung function, specifically the PF ratio, is a major determinant of the maximal PbtO₂ attained during an oxygen challenge.

Conclusions. Given that patients with TBI are at risk for pulmonary complications such as pneumonia, severe atelectasis, and adult respiratory distress syndrome, lung function must be considered when interpreting brain tissue oxygenation. (DOI: 10.3171/JNS/2008/108/01/0059)

Key Words • brain tissue oxygenation • PF ratio • pulmonary function • traumatic brain injury

DIRECT monitoring of PbtO₂ is a widely available tool that allows for assessment of cerebral oxygenation after brain injury. Previous studies have demonstrated that low PbtO₂ is associated with higher mortality rates and poorer functional outcome.⁶,¹⁶,¹⁷ The fact that lower levels of PbtO₂ and a longer duration of low PbtO₂ influence outcome suggests a dose–response relationship and has led some investigators to consider using interventions that increase PbtO₂, such as raising FiO₂ concentrations, as part of an overall “oxygen-directed” therapeutic strategy after TBI.⁵,⁸ Additionally, prior studies have suggested that the rate, or pattern, of rise in PbtO₂ in response to an increase in FiO₂ concentration, a so-called “oxygen challenge,” is indicative of prognosis after head trauma.¹⁸,¹⁹ A recent study has shown improved outcomes in patients with severe TBI who were treated with an oxygen-directed protocol designed to maintain PbtO₂ above threshold levels, compared with historical controls.¹⁶ These studies did not specifically address the pulmonary status of patients with commonly used indices of lung function, however, such as the ratio of PaO₂ to FiO₂ (the PF ratio).

Although it may appear obvious that pulmonary disease might influence PbtO₂, previous studies have not systematically explored the nature of this relationship. Our clinical experience with patients with severe TBI who underwent PbtO₂ monitoring suggested that in many cases the cause of low PbtO₂ appeared to be related to low PaO₂ resulting from pulmonary disease. Oxygen-directed therapy is currently under consideration for use in TBI; therefore, it appears important to more clearly delineate the influence of
pulmonary function on steady-state PbtO₂ during an oxygen challenge. In critically ill patients, end-organ oxygenation is often influenced by the ability of the lung to oxygenate arterial blood. To reach the brain, oxygen must diffuse from the alveolar air across the lung into the blood, and from the blood across the blood–brain barrier into the brain. A barrier to effective diffusion may occur either across the lung because of ventilation perfusion mismatch or across the blood–brain barrier due to cerebral factors.

The purpose of our study was to prospectively evaluate whether PbtO₂ during an oxygen challenge is influenced by noncerebral factors related to systemic oxygenation, such as PaO₂, FiO₂, and pulmonary function as represented by the PF ratio. Previous studies have proposed that the changes observed following an oxygen challenge might be related primarily to the brain’s metabolic needs. Based on our clinical experience, we hypothesized that the PF ratio strongly influences PbtO₂ during an oxygen challenge and that this effect is mediated primarily through changes in arterial oxygen tension, rather than through exclusively cerebral factors.

### Clinical Material and Methods

#### Patient Population

Thirty-seven consecutive patients admitted to San Francisco General Hospital with severe head injury defined as a Glasgow Coma Scale score ≤ 8 or a head injury in combination with multisystem injury requiring ICP monitoring were included in this study. All patients with intracranial hematomas requiring removal underwent urgent surgical evacuation. Monitoring of ICP was performed using an external ventricular drain or an intraparenchymal ICP monitor (Camino, Integra Lifesciences). Patients were treated in accordance with standard guidelines for the management of severe TBI.¹ Clinical outcome was determined using the score on the GOS 6 months postinjury. This study was approved by the University of California, San Francisco, Committee for Human Research.

#### Brain Tissue Oxygen Monitoring

All patients underwent insertion of a Licox intraparenchymal brain tissue oxygen monitor (Integra Lifesciences) as part of the standard neurointensive care for patients with severe TBI at our institution. Monitors were inserted in patients in the ICU while they were intravenously sedated and after local anesthesia was induced (1% lidocaine). Licox probes were inserted over the Kocher point into the frontal lobe of the least injured hemisphere. Probes were allowed to stabilize for at least 12 hours following insertion before any oxygen challenge was performed. Follow-up computed tomography scans were obtained to confirm that the Licox probe was not in contused or infarcted tissue.

#### Oxygen Challenge

At our institution, an oxygen challenge is performed daily as part of regular clinical care to evaluate the function and responsiveness of the brain tissue oxygen probe. The oxygen challenge involves increasing the FiO₂ concentra-

### Results

Sixty-nine oxygen challenges were performed in 37 consecutive patients with TBI. Patient characteristics are detailed in Table 1. Mean FiO₂, PF ratio, hemoglobin, MAP, ICP, CPP, PaO₂, PaCO₂, and PbtO₂ values before and after the oxygen challenge are detailed in Table 2.

As expected, the baseline PF ratio was strongly correlated with postchallenge PaO₂ (r = 0.84, p < 0.0001; Fig. 1), indicating that patients with better pulmonary function attain higher arterial oxygen tension during an oxygen challenge. Each 50-point increase in the baseline PF ratio translated to a 26 mm Hg higher challenge PaO₂ (p < 0.001). This result is not surprising given that the response to an oxygen challenge is greatly dependent on the relative increase in FiO₂ concentration. Patients with poor baseline pulmonary function (PF ratio ≤ 250) were ventilated at a mean FiO₂ of 0.54 ± 0.13, whereas those with a PF ratio > 250 were ventilated at a mean FiO₂ of 0.40 ± 0.09 to main-

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¹ Clinical outcome was determined using the score on the GOS 6 months postinjury. This study was approved by the University of California, San Francisco, Committee for Human Research.
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As anticipated from the relationships between the PF ratio, PaO₂, and PbtO₂, we found a significant relationship between baseline PF ratio and challenge PbtO₂ (r = 0.41, p < 0.001). To further evaluate the effect of pulmonary status on brain tissue oxygenation, we compared baseline and challenge PbtO₂ in patients with a PF ratio > 250 with those patients with a PF ratio ≤ 250 (Fig. 3). At baseline, no significant difference in PbtO₂ was noted between patients with a PF ratio > 250 and those with a PF ratio ≤ 250 (29.5 ± 12.4 mm Hg and 29.6 ± 12.8 mm Hg, respectively; p = 0.99). During the oxygen challenge, patients with a PF ratio > 250 attained a mean PbtO₂ of 97.8 ± 45.6 mm Hg, compared with a mean PbtO₂ of 66.4 ± 30.2 mm Hg in patients with a PF ratio ≤ 250 (p < 0.005), implicating pulmonary status as an important influence on peak steady-state PbtO₂ attained with an oxygen challenge. There was no significant difference in mean hemoglobin level, MAP, ICP, CPP, or PaCO₂ between patients with a PF ratio ≤ 250 compared with those with a PF ratio > 250, either at baseline or during oxygen challenge (Table 3).

Importantly, differences in pulmonary function appeared to influence the pattern of response of PbtO₂ to an oxygen challenge. Figure 4A demonstrates the pattern of the rise in brain tissue oxygen in a patient with severe TBI with a baseline PF ratio > 250 attained a mean PbtO₂ of 97.8 ± 45.6 mm Hg, compared with a mean PbtO₂ of 66.4 ± 30.2 mm Hg in patients with a PF ratio ≤ 250 (p < 0.005), implicating pulmonary status as an important influence on peak steady-state PbtO₂ attained with an oxygen challenge. There was no significant difference in mean hemoglobin level, MAP, ICP, CPP, or PaCO₂ between patients with a PF ratio ≤ 250 compared with those with a PF ratio > 250, either at baseline or during oxygen challenge (Table 3).
pulmonary function. In contrast, an oxygen challenge performed in the same patient 2 days later at a similar baseline FiO\textsubscript{2} of 0.30, but a decreased baseline PF ratio of 223, revealed a markedly different pattern of response (Fig. 4B). The magnitude of increase in PbtO\textsubscript{2} is blunted and occurs over a much longer time course of ~15–20 minutes. The change in response occurred concomitantly with the development of V\textsubscript{AP} in this patient, suggesting that the pattern of increase as well as the steady-state value of brain tissue oxygen following an oxygen challenge is influenced by pulmonary function.

Of the 37 patients in our series, V\textsubscript{AP} (as defined by the National Nosocomial Infection Surveillance criteria\textsuperscript{10,11}) was diagnosed in 11 (30\%) around the time of the oxygen challenge. Of these patients with V\textsubscript{AP}, 100\% had a PF ratio \leq 250 at the time of diagnosis. Although a greater number of patients in our series (17 patients, 46\%) had atelectasis on chest radiographs, only 4 of these patients (24\%) had a PF ratio of \leq 250. Three patients who developed V\textsubscript{AP} had atelectasis that preceded the development of V\textsubscript{AP}. Two patients with V\textsubscript{AP} also met criteria for ARDS. Two patients also had significant pulmonary contusions from the initial injury in addition to V\textsubscript{AP}, and 1 patient had pulmonary contusions without other pulmonary disease also resulting in a PF ratio \leq 250. A pulmonary embolism was not diagnosed in any patient. Sixteen patients had a PF ratio \leq 250 during the time an oxygen challenge was performed. Several patients had worsening PF ratios and more blunted responses to an oxygen challenge during the course of the ICU hospitalization as pulmonary diseases developed.

Although the purpose of this study was to define the physiological relationship between lung function and PbtO\textsubscript{2}, 6-month outcome was also assessed. Thirteen (35.1\%) of 37 patients had a favorable outcome, defined as a GOS score of 4–5, 6 months after injury. The overall mortality rate at 6 months was 18.9\%. Two patients (5.4\%) were lost to follow-up. There was no significant relationship between baseline PF ratio and outcome (p = 0.58). Given the previously published work of van Santbrink and associates,\textsuperscript{19} we also calculated TOR in all our patients. In contrast to the results of van Santbrink and colleagues, we found no significant relationship between baseline PF ratio and outcome (p = 0.58). Given the previously published work of van Santbrink and associates,\textsuperscript{19} we also calculated TOR in all our patients. In contrast to the results of van Santbrink and colleagues, we found no significant relationship between TOR and outcome (p = 0.99). Our smaller sample size, however, may not have been sufficiently powered to show a difference.

**Discussion**

Previous studies have demonstrated that low PbtO\textsubscript{2} is

![Fig. 3](image.png)

**Fig. 3.** Bar graph showing a comparison of patients with PF ratios \leq 250 or \geq 250 and their corresponding PbtO\textsubscript{2} levels at baseline and after the oxygen challenge. The baseline PF ratio is associated with steady-state PbtO\textsubscript{2} during an oxygen challenge. The PbtO\textsubscript{2} level during an oxygen challenge is greater in those patients with a PF ratio > 250 than in those with a PF ratio \leq 250, suggesting an important influence of lung function on brain tissue oxygenation. *p < 0.005.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline PF \leq 250</th>
<th>Baseline PF &gt;250</th>
</tr>
</thead>
<tbody>
<tr>
<td>\text{FiO}_2</td>
<td>0.54 ± 0.13</td>
<td>0.40 ± 0.09†</td>
</tr>
<tr>
<td>PF ratio</td>
<td>192 ± 36</td>
<td>379 ± 87†</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>10.6 ± 0.9 mg/dl</td>
<td>10.8 ± 0.9 mg/dl</td>
</tr>
<tr>
<td>MAP</td>
<td>91 ± 15 mm Hg</td>
<td>92 ± 12 mm Hg</td>
</tr>
<tr>
<td>CPP</td>
<td>13 ± 5 mm Hg</td>
<td>12 ± 5 mm Hg</td>
</tr>
<tr>
<td>PaCO\textsubscript{2}</td>
<td>79 ± 15 mm Hg</td>
<td>80 ± 12 mm Hg</td>
</tr>
<tr>
<td>PaCO\textsubscript{2}</td>
<td>39 ± 5 mm Hg</td>
<td>38 ± 4 mm Hg</td>
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* Values are expressed as means ± SDs.
†p < 0.001.
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predictive of poor outcome after severe head trauma. Furthermore, investigators have suggested that this correlation is related to both the depth and duration of brain tissue hypoxia. Prevention and treatment of brain tissue hypoxia is now being strongly considered, and some investigative groups have already described their initial results with oxygen-directed therapy designed to maintain PbtO2 above a certain threshold. Meixensberger and colleagues used a CPP-directed strategy to maintain PbtO2 > 10 mm Hg in 93 patients with severe TBI. Stiefel et al. used a multifaceted protocol to maintain PbtO2 > 25 mm Hg in 28 patients with severe TBI, comparing outcomes with those from historical controls. Although maintaining PbtO2 above threshold levels is important, we believe that it is also imperative to identify the specific cause of low PbtO2 in a given patient with TBI, as many systemic or cerebral factors may be responsible for a decline in cerebral oxygenation at a particular instance. Our data suggest that lower PbtO2 values during an oxygen challenge may indicate primary pulmonary disease (such as atelectasis, pneumonia, or pulmonary contusion) that may require treatment itself. Pulmonary problems commonly occur in patients with TBI. In our series, 43% of patients had a PF ratio ≤ 250 during the portion of the ICU course in which oxygen challenge was performed, which was due to VAP, severe atelectasis, pulmonary contusions, ARDS, or a combination of these conditions. In a prior study, acute lung injury occurred in 31% of patients with severe TBI and independently predicted a poorer outcome. Notably, in a prior trial of cerebral blood flow–directed therapy in TBI, a 5-fold increase in the incidence of ARDS may have offset a beneficial effect of improved global cerebral oxygenation. As oxygen-directed therapy is further evaluated for TBI, it will be necessary to consider patient pulmonary status when planning interventions to maximize brain tissue oxygenation, either as part of a clinical trial or for regular clinical care.

During neuromonitoring after severe brain injury, important information may be gained by challenging a physiological system. At our institution, as in many others, baseline PaO2 is maintained at a level of ~ 100 mm Hg in patients with severe TBI. Patients with poor systemic oxygenation may be treated by increasing FiO2, or the peak expiratory pressure to maintain this PaO2 goal. When such interventions succeed in maintaining PaO2 at a level of ~ 100 mm Hg, PbtO2 will often remain in the normal range, even in patients with poor pulmonary status. When an intervention such as an oxygen challenge is performed, the important influence of lung function on brain tissue oxygenation becomes evident. Our results suggest that those patients with better pulmonary status have higher PbtO2 with an oxygen challenge than those with compromised pulmonary function (Fig. 3). The peak PbtO2 during an oxygen challenge is likely influenced by the peak PaO2 during the challenge (Fig. 2). Intuitively, it is understandable that those patients with better pulmonary function will have a higher PaO2 level during an oxygen challenge compared with those patients with poor pulmonary function, and this may influence PbtO2 in these patients. Our findings confirm this expected relationship and implicate pulmonary status as an important influence on peak PbtO2 in an oxygen challenge.

Given that systemic oxygenation and brain tissue oxygenation are strongly linked through the relationships between oxygen transport through the lungs and to the brain, the care of patients with brain injury should rightly consider the interplay between both. Some investigative groups have proposed normobaric hyperoxia (an increase in FiO2 to 1.0) as a treatment strategy to improve cerebral oxygenation in patients with severe TBI. Tofias and associates studied the cerebral metabolic profile of 52 patients with severe TBI who underwent measurements with microdialysis. These investigators found a decrease in lactate, glucose, and lactate/pyruvate ratio in patients treated with normobaric hyperoxia, compared with historical controls. Although the improved cerebral metabolic profile they describe may potentially benefit the injured brain, it is important to consider that in patients with pulmonary pathology, an increase in FiO2 may not lead to the same degree of improved cerebral oxygenation. Our data suggest that patients with a low PF ratio will have a relatively lower
PbtO₂ at an FiO₂ of 1.0, implying that this treatment strategy may not be as effective in patients with TBI and severe pulmonary pathology.

In a prior study, van Santbrink and associates described an association between TOR and 6-month GOS scores. In our study, we did not find a relationship between TOR and 6-month outcome scores. Although it is possible that our study was underpowered to detect this relationship, it may be that the response of the brain to an oxygen challenge as measured by TOR is not a particularly informative indicator of brain injury that predicts long-term functional disability. Additionally, van Santbrink and colleagues reported that different patterns of increase in PbtO₂ during oxygen challenge was predictive of outcome, but they did not describe the influence of pulmonary status (such as the PF ratio) on these PbtO₂ response patterns. Because the PF ratio strongly influences PbtO₂ during oxygen challenge, we are concerned that these patterns may primarily be indicators of the pulmonary status of the patient, rather than indicators of the brain’s own ability to respond to an oxygen challenge (Fig. 4). Certainly, we urge caution in using these patterns as a guide for neurological prognosis and believe that they may represent the complex interplay between the lung and brain. Because patients with TBI may suffer a primary injury to the chest wall and lung as part of their initial injury and are at risk for aspiration and VAP, it appears prudent to consider pulmonary status when interpreting results of a systemic oxygen challenge.

Our study has several limitations, including a small sample size for correlation with outcome. We did not set out to evaluate the relationship between PbtO₂ during an oxygen challenge and outcome, but rather to better define the physiological parameters leading to a poor response to an oxygen challenge. Nevertheless, future studies will need to address whether targeted treatment to improve low PbtO₂ by treating pulmonary diseases improves outcome in patients with severe TBI. An additional limitation of our study is that assessing the response to an oxygen challenge is inherently constrained by the ability to increase the FiO₂ to 1.0. This limits the ability to compare the absolute rise in PbtO₂ between patients with different baseline FiO₂ concentrations that may reflect their initial pulmonary status. Beginning the challenge at the same FiO₂ level regardless of pulmonary status may adversely affect patient care and was deemed imprudent by our group. Although it is not possible to compare absolute response to an oxygen challenge between patients due to the different baseline FiO₂ levels, the steady-state PbtO₂ during a challenge may be compared between patients, yielding potentially important information on the influence of pulmonary status on PbtO₂.

Lastly, our study did not systematically investigate the temporal relationship between the PF ratio and PbtO₂ throughout the ICU time course. We evaluated the relationship between the PF ratio, PaO₂, and PbtO₂ at different time points after injury in our patients. Future studies may seek to study the temporal relationship between these variables. Better defining the interrelationships between pulmonary and cerebral variables influencing cerebral oxygenation may lead to effective targeted therapeutic strategies to prevent episodes of low PbtO₂.

Conclusions

The PF ratio strongly influences PbtO₂, with an oxygen challenge in patients with severe TBI. In patients with TBI, a low PF ratio is associated with lower PbtO₂ during an oxygen challenge. Given that patients with severe TBI are at risk for pulmonary complications including pneumonia, severe atelectasis, and ARDS, pulmonary status should be considered when interpreting brain tissue oxygen.

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References

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