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ORIGINAL ARTICLE

The Effect of Increased Inspired Fraction of Oxygen on Brain Tissue Oxygen Tension in Children with Severe Traumatic Brain Injury

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Abstract
Background This study examines the effect of an increase in the inspired fraction of oxygen (FiO_2) on brain tissue oxygen (PbO_2) in children with severe traumatic brain injury (TBI).
Methods A prospective observational study of patients who underwent PbO_2 monitoring and an oxygen challenge test (temporary increase of FiO_2 for 15 min) was undertaken. Pre- and post-test values for arterial partial pressure of oxygen (PaO_2), PbO_2, and arterial oxygen content (CaO_2) were examined while controlling for any changes in arterial carbon dioxide tension and cerebral perfusion pressure during the test. Baseline transcranial Doppler studies were done. Outcome was assessed at 6 months.
Results A total of 43 tests were performed in 28 patients. In 35 tests in 24 patients, the PbO_2 monitor was in normal-appearing white matter and in eight tests in four patients, the monitor was in a pericontusional location. When catheters were pericontusional or in normal white matter the baseline PbO_2/PaO_2 ratio was similar. PaO_2 ($P < 0.0001$) and PbO_2 ($P < 0.0001$) significantly increased when FiO_2 was increased. The magnitude of the PbO_2 response (ΔPbO_2) was correlated with ΔPaO_2 ($P < 0.0001$, $R^2 = 0.37$) and ΔCaO_2 ($P = 0.001$, $R^2 = 0.23$). The $\Delta PbO_2/\Delta PaO_2$ ratio (oxygen reactivity) varied between patients, was related to the baseline PbO_2 ($P = 0.001$, $r = 0.54$) and was inversely related to outcome ($P = 0.02$, confidence interval 0.03–0.78).
Conclusion Normobaric hyperoxia increases PbO_2 in children with severe TBI, but the response is variable. The magnitude of this response is related to the change in PaO_2 and the baseline PbO_2. A greater response appears to be associated with worse outcome.

Keywords Brain tissue oxygen tension · Arterial oxygen tension · Children · Traumatic brain injury · Outcome

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Introduction

Brain tissue oxygen tension (PbO_2) monitoring is used more frequently in adult traumatic brain injury (TBI) to

supplement intracranial pressure (ICP) and cerebral perfusion (CPP) monitoring to guide treatment. Reduced PbO_2 is associated with poor outcome and so management protocols to maintain PbO_2 above a threshold of 15–20 mmHg are recommended [1–5]. The associations between PbO_2 and outcome, and the determinants of PbO_2, are less well studied in pediatric TBI [6, 7]. In particular, the relationship between arterial oxygen tension (PaO_2) and PbO_2 in children, and the implications of this relationship, have not been examined.

What determines PbO_2 is only beginning to be elucidated [8]. In experimental and clinical studies, PbO_2 is associated variably with systemic factors such as arterial saturation and blood pressure, and local factors such as ICP, CPP, cerebral blood flow (CBF), cerebral metabolic rate of oxygen, product of blood flow and oxygen content, mean transit time of blood through the brain, end-capillary venous oxygen tension, and arteriovenous difference of oxygen [8–16]. These studies suggest that PaO_2 may strongly influence PbO_2; however, the PbO_2 response to increased PaO_2 varies between patients. The determinants and significance of the magnitude of this PbO_2 response are unclear and while normobaric hyperoxia may correct compromised PbO_2 and possibly improve brain metabolism, its overall benefits are not known [17–19]. However, the benefits of hyperoxia for brain metabolism and PbO_2 are not inevitable [20]. This is important since there is a well-described association between reduced PbO_2 and poor outcome in adults and children [1–5] whereas hyperoxia is known to have potential deleterious side-effects to both the lungs and to the brain [21–24]. The effects of hyperoxia on PbO_2 in pediatric TBI are unknown since studies that have examined this question to date are in adult patients. Therefore, in this study we examined children with severe TBI to determine (1) the relationship between increased PaO_2 and PbO_2, and (2) the association of this relationship with clinical outcome.

Methods and Materials

Patient Selection

Ethics approval for the study was obtained from the institutional review boards of the University of Cape Town and the Red Cross War Memorial Children's Hospital. Consent was taken from the child's closest relative for inclusion in the study.

Patient Selection

All patients considered for inclusion in the study received ICP and PbO_2 monitors. This study was part of a larger prospective observational study of intracranial monitoring in children with TBI. In this study, we collected data from all consecutive children (age <15 years old) with severe TBI (Glasgow Coma Score ≤ 8) and who received a PbO_2 monitor and an oxygen challenge test (OCT). OCTs were included in the study only if the patient (1) was hemodynamically stable, (2) had the PbO_2 monitor in situ for more than 12 h, (3) had a stable PbO_2 signal, (4) did not have vasospasm (diagnosed with Lindegaard's ratio on transcranial Doppler, TCD), and (5) had a PbO_2 catheter placed in normal-appearing white matter on the head CT scan.

ICP and PbO_2 Monitors

ICP was measured with an intraparenchymal monitor [Codman ICP Express (Codman, Raynham, MA) or Camino (Integra Neurosciences, Plainsboro, NJ)]. When an ICP monitor was placed, we also monitored and treated PbO_2. PbO_2 monitors (Licox®, Integra Neurosciences, Plainsboro, NJ) were inserted into normal-appearing right frontal white matter if there were no localized lesions, or in the hemisphere with the greater swelling or containing focal lesions. The position of the monitor was confirmed on follow-up head computed tomography (CT). PbO_2 catheters were allowed to stabilize and OCTs were included in the study only if performed >12 h after catheter insertion.

Patient Management

Patient care was based on a local protocol consistent with the current recommendations for the management of severe TBI in children. Briefly, all patients were resuscitated on admission, underwent immediate evacuation of space-occupying lesions when present, and were intubated and mechanically ventilated in the pediatric intensive care unit (ICU). Elevated ICP was treated using a stepwise approach when ICP was >20 mmHg according to the guidelines for ICP management in children [25, 26]. We aimed to keep CPP $>$ 50 mmHg in children >2 years old, and >45 mmHg in children <2 years old. Compromised (low) PbO_2 was defined as <20 mmHg and was treated using a hierarchical treatment algorithm based on the possible cause for low PbO_2. Further details of our ICP and PbO_2 management are described elsewhere [6].

Oxygen Challenge Tests

OCTs were part of regular clinical care to test the response of the PbO_2 monitor and were performed by increasing the

inspired fraction of oxygen (FiO_2) setting on the ventilator for 15 min. Pre- and post-test data, including the PbO_2 response, were collected. OCTs were included in this study if the following values were recorded: (1) pre- and post-test values for PbO_2, ICP, CPP, PaO_2, arterial saturation (SaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), and (2) baseline values for hemoglobin (Hb) and Transcranial Doppler (TCD) mean flow velocity of the middle cerebral artery (FV_{MCA}) recorded from the hemisphere with the PbO_2 monitor. TCD studies were performed using a standard TCD machine and 2 MHz probe (Smart-Lite^{TM}, Rimed, Raanana, Israel). The highest mean flow velocity obtained for the MCA was recorded. Principal analysis was performed only on OCT data obtained from PbO_2 catheters placed in normal-appearing white matter on head CT scan because of different physiological changes in pericontusional locations. These results also were compared to data obtained from pericontusional PbO_2 probes.

Physiological Data

An arterial sample was taken before the FiO_2 increase (before test) and after 15 min at the higher FiO_2 (after test). The oxygen content (CaO_2) of arterial samples was calculated from the equation:

$$CaO_2(\text{ml } O_2/100\,\text{ml}) = (\text{Hb} \times 1.36 \times SaO_2) + (0.0031 \times PaO_2).$$

Differences between before and after OCT (after 15 min at the increased FiO_2 level) values were recorded as ΔPbO_2, ΔPaO_2, ΔCaO_2, $\Delta PaCO_2$, and ΔCPP. FiO_2 was increased to 100% in most but not all patients. In the early part of this series, FiO_2 was increased by 0.1 above the baseline for 15 min ($n = 5$ tests), while in the latter part of the series we adjusted our protocol to increase the FiO_2 to 100% for 15 min ($n = 38$ tests). Because the baseline FiO_2 also differed between patients, the ratio of the change in PbO_2 for the change in PaO_2 ($\Delta PbO_2/\Delta PaO_2$) was calculated to assess the response of PbO_2 to the change in PaO_2; therefore, data from all tests could be used. The $\Delta PbO_2/\Delta PaO_2$ was termed the oxygen reactivity, and was used as the key variable against which other factors were tested for association.

Outcome

Clinical outcome was assessed at 6 months after injury using the Glasgow Outcome Score (GOS) which was dichotomized to unfavorable (GOS 1–3) and favorable (GOS 4–5) outcome. We chose the GOS since we have observed similar outcome results when using the dichotomized GOS or the dichotomized Pediatric Cerebral Performance Category Scale [4].

Statistical Analysis

All data were analysed with R statistical computing (http://wwww.r-project.org). Variables were tested for normality with the Shapiro–Wilk test. Differences between the before test and after test values for PaO_2 and PbO_2 were examined with the Wilcoxon's rank sum test. The relationship between ΔPaO_2 and ΔPbO_2 was examined with Spearman's correlation and Pearson's product–moment correlation. Correlation coefficients are reported as r. Linear regression was used to examine the relationship between ΔPbO_2 and ΔPaO_2 and ΔCaO_2 while controlling for ΔCO_2 and ΔCPP. Since multiple studies in some patients were analysed, we used a general estimating equation (GEE) to account for inter-individual differences between tests with catheters placed in normal-appearing brain and those located near contusions for baseline values and $\Delta PbO_2/\Delta PaO_2$ and for the analysis of data in Group A. Linear regression was used to examine the relationship between $\Delta PbO_2/\Delta PaO_2$ and the following factors: baseline PbO_2, baseline CPP, FV_{MCA}, ΔCaO_2, and day of testing (post-injury day; first 24 h = day 1). Coefficients for relationships between $\Delta PbO_2/\Delta PaO_2$ and other variables were checked with nonparametric bootstrap methods to correct for repeat measures. $\Delta PbO_2/\Delta PaO_2$ was further examined for relationships with outcome (using the GOS) and other parameters of PbO_2 that were recorded for the whole duration of the monitoring period. This included the duration of time that PbO_2 was <10 mmHg, the mean PbO_2 in the first 24 h of monitoring ($mPbO_{2\ 24}$) and the lowest PbO_2 recorded for each patient. $\Delta PbO_2/\Delta PaO_2$ also was examined with log transformation to ensure that the normality assumption was met. Results are expressed as mean ± SD or median and interquartile range (IQR) and range. Significance was set at $P = 0.05$.

Results

Patient Characteristics

A total of 43 tests in 28 patients were performed for which all required data were available. There were 24 patients ($n = 35$ tests) who had catheters placed in normal-appearing white matter (group A) and 4 patients ($n = 8$ tests) who had catheters placed close to contusions on (Group B). Head CT scans on these patients showed that the probe was placed close to the contusion but not obviously within it. Baseline variables for all patients are summarized in Table 1. For patients in Group A, baseline PbO_2 was <15 mmHg at the time of testing in 3 of 35 tests (8.5%) and <10 mmHg in 1 (2.9%).

Table 1 Baseline variables for patients

Characteristic	Value
Age	5.8 ± 0.6 years (range 9 months–11 years)
Day of testing	Day 3 (1.5–5) range 1–9
Baseline PaO_2	155.7 ± 9.2 mmHg (range 58–332)
Baseline PbO_2	31.3 (25.2–38.8) range 8–81 mmHg
Baseline PbO_2/PaO_2 (%)	24.6 ± 1.7% (range 3.9–50.5)
TCD FV_{MCA}	103 ± 4.1 cm/s (range 59–154)
Baseline CPP	69 ± 1.8 mmHg (range 42–98 mmHg)

Results for baseline variables for all patients and tests. Results are reported as mean ± standard error of the mean (range) or median (IQR) and range depending on distribution. *Day of testing* post-injury day of the hyperoxia test (day 1 = first 24 h), *PbO_2* partial pressure of brain tissue oxygen, *PaO_2* partial pressure of arterial oxygen, *TCD FV_{MCA}* mean flow velocity of the middle cerebral artery, *CPP* cerebral perfusion pressure

PbO_2 Responses in Normal-Appearing Tissue (Group A) and Pericontusional Locations (Group B)

OCT results in Group A and B were tested for differences in PaO_2, PbO_2, PbO_2/PaO_2, $\Delta PbO_2/\Delta PaO_2$, CPP, and FV_{MCA}. The baseline FV_{MCA} in Group B was slightly lower ($P = 0.045$) (Fig. 1). $\Delta PbO_2/\Delta PaO_2$ was slightly higher in Group B ($P = 0.049$) but not when controlled for baseline PbO_2/PaO_2 ($P = 0.055$). There were no significant differences for PbO_2 ($P = 0.08$), PbO_2/PaO_2 ($P = 0.98$), PaO_2 ($P = 0.07$), or baseline CPP ($P = 0.48$) (Table 2). The remaining analysis below applies to Group A.

Effect of increased FiO_2 on PaO_2 and PbO_2 (Group A)

Baseline PaO_2 and PbO_2 were not significantly related ($P = 0.3271$). Induced hyperoxia significantly increased both PaO_2 ($P < 0.0001$) and PbO_2 ($P < 0.0001$). There was a significant relationship between ΔPbO_2 and ΔPaO_2 ($P < 0.0001$, $R^2 = 0.371$). This relationship was maintained when controlled for ΔCO_2 and ΔCPP ($P < 0.0001$, $R^2 = 0.412$) during the test. ΔPbO_2 and ΔCaO_2 were also significantly related ($P = 0.001$, $R^2 = 0.232$).

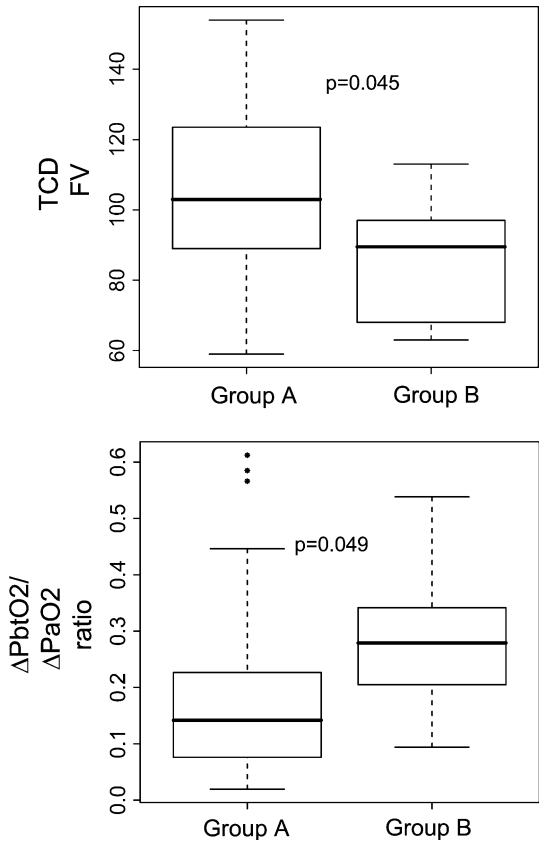

Fig. 1 Boxplots for TCD FV_{MCA} (*above*) and $\Delta PbO_2/\Delta PaO_2$ ratio (*below*) for Group A (PbO_2 in normal-appearing white matter on head CT scan; $n = 24$ patients and 35 tests) and Group B (PbO_2 probe pericontusional on head CT scan; $n = 4$ patients and eight tests)

Physiological Factors and $\Delta PbO_2/\Delta PaO_2$ (Group A)

$\Delta PbO_2/\Delta PaO_2$ was significantly correlated with baseline PbO_2 (Spearman's $r = 0.538$, $P = 0.001$; linear regression $P < 0.0001$) (Fig. 2). Table 3 describes the relationships between $\Delta PbO_2/\Delta PaO_2$ and other physiological factors.

Table 2 Differences between variables in Group A (PbO_2 catheters in normal-appearing tissue) and Group B (PbO_2 catheters in pericontusional tissue)

Variable	Group A ($n = 35$ tests)	Group B ($n = 8$ tests)	P value
Baseline PbO_2	30.6 (23.7–37.3)	39.4 (32.3–52)	0.08
Baseline PaO_2	154.3 (95.8–179.7)	212.8 (139.5–228.2)	0.07
Baseline PbO_2/PaO_2 (%)	24.1 (17.9–30.5)	27.0 (15.1–31.0)	0.98
Baseline CPP	68 (61–75)	73 (67–77)	0.48
Baseline FV_{MCA}	103 (89.5–123)	89.5 (72.5–96)	0.045
$\Delta PbO_2/\Delta PaO_2$ (%)	14.2 (7.6–22.7)	27.9 (21.9–32.5)	0.049

Values are reported as median (IQR). Analysis corrects for repeat measures. *PbO_2* partial pressure of brain tissue oxygen, *PaO_2* partial pressure of arterial oxygen, *FV_{MCA}* mean flow velocity of the middle cerebral artery, *CPP* cerebral perfusion pressure

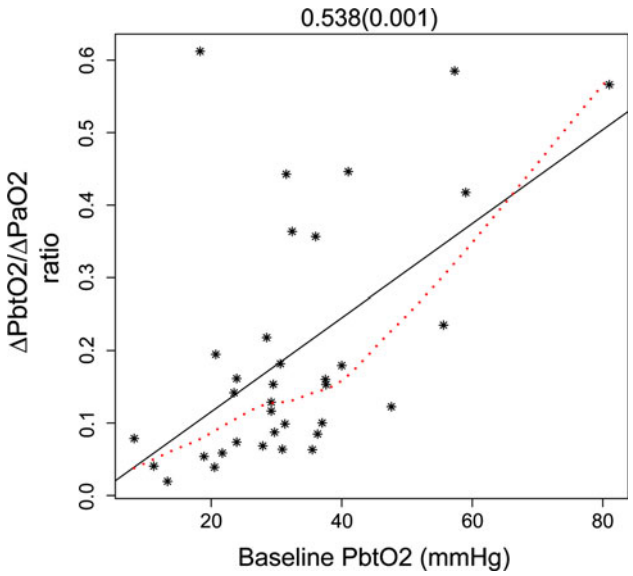

Fig. 2 Scatterplot diagram of $\Delta PbO_2/\Delta PaO_2$ and Baseline PbO_2 for Group A patients (PbO_2 probe in normal-appearing white matter on head CT scan). Above the box is the Spearman's coefficient (*P* value)

Table 3 Relationships between $\Delta PbO_2/\Delta PaO_2$ and other physiological factors for Group A patients (PbO_2 probe in normal-appearing white matter on head CT scan)

Variable	Coefficient	*P* value
Baseline PbO_2	0.54	<0.001
Baseline PaO_2	−0.3	0.87
Baseline CPP	0.19	0.27
FV_{MCA}	0.14	0.44
ΔCaO_2	0.07	0.7
PT day	0.36	0.03

Results were similar when corrected for repeated measures. *PbO_2* partial pressure of brain tissue oxygen, *PaO_2* partial pressure of arterial oxygen, *FV_{MCA}* mean flow velocity of the middle cerebral artery, *CPP* cerebral perfusion pressure, *ΔCaO_2* change in arterial oxygen content, *PT day* post-trauma day

$\Delta PbO_2/\Delta PaO_2$ was not correlated with baseline CPP ($P = 0.27$), baseline FV_{MCA} ($P = 0.44$), or ΔCaO_2 ($P = 0.70$). It was however, significantly correlated with the post-trauma day ($r = 0.36$, $P = 0.03$), i.e., greater $\Delta PbO_2/\Delta PaO_2$ values were found with increasing day after injury, but not when adjusted for baseline PbO_2 ($P = 0.95$). There were no significant relationships between $\Delta PbO_2/\Delta PaO_2$ and other markers of low PbO_2 for the duration of monitoring for each patient, including $PbO_2 < 10$ mmHg, mean PbO_2 for the first 24 h, and the lowest PbO_2.

Outcome (Group A Patients; $n = 24$)

Outcome was as follows: GOS 1 [died] ($n = 3$, 12.5%); GOS 2 ($n = 0$); GOS 3 ($n = 4$, 16.7%); GOS 4 ($n = 7$, 29.2%); GOS 5 ($n = 10$, 41.7%). $\Delta PbO_2/\Delta PaO_2$ was inversely related to dichotomized outcome, with and without log transformation of $\Delta PbO_2/\Delta PaO_2$. This relationship remained significant when adjusted for baseline PbO_2, day of testing and age ($P = 0.02$, 95% confidence interval 0.03–0.78) (Table 4). Therefore, a greater $\Delta PbO_2/\Delta PaO_2$ was associated with a lower probability of favorable outcome.

Table 4 Results of multivariate logistic regression analysis for relationship between variables and dichotomized outcome for Group A patients (PbO_2 probe in normal-appearing white matter on head CT scan)

	Estimate	SE	*P* value	95% Confidence interval
$\Delta PbO_2/PaO_2$	−1.839	0.811	0.023	0.03–0.78
Baseline PbO_2	0.057	0.042	0.170	0.98–1.15
PT day	−0.265	0.231	0.251	0.49–1.21
Age	−0.148	0.152	0.332	0.64–1.16

SE Standard error of the mean, *PT day* day of testing post-injury, *PbO_2* partial pressure of brain tissue oxygen, *PaO_2* partial pressure of arterial oxygen. Log transformation was used to create a normal distribution of $\Delta PbO_2/PaO_2$

Discussion

In this study, we examined the effect of a temporary increase of FiO_2 on PbO_2 in children with severe TBI. The main findings were: (1) induced normobaric hyperoxia significantly increased PbO_2, (2) the magnitude of this increase was closely associated with the change in PaO_2, (3) the response of PbO_2 for the given change in PaO_2 ($\Delta PbO_2/\Delta PaO_2$, or O_2 reactivity) was increased when baseline PbO_2 was higher, and (4) a greater PbO_2 response to PaO_2 change (higher $\Delta PbO_2/\Delta PaO_2$) was associated with worse outcome.

Methodological Limitations

There are several potential limitations in this study. First, the sample size was small; therefore some significant relationships may not have been demonstrated; therefore these should be regarded as preliminary results. However, despite the limited sample size several significant results were found. The results of this study however, require replication in a larger study. Second, TCD-derived FV_{MCA} was recorded but not local CBF. FV_{MCA} is a good surrogate marker of changes of MCA CBF [27, 28] but does not necessarily reflect local CBF. Since PbO_2 is a measure of local oxygen tension, local measures of CBF may have been better suited to this study. Third, the increase in FiO_2 was not standardized. However, PaO_2 varies in response

even to a standard FiO_2 increase and in this study PbO_2 changes were interpreted relative to the magnitude of change in PaO_2, not the FiO_2 increase; therefore, the relative changes are valid for analysis. Fourth, we did not measure jugular venous saturation ($SJVO_2$) and so we cannot comment on the relationship between PbO_2 and the arteriovenous difference in oxygen content [8]. Fifth, we did not measure cerebral metabolism; therefore, we cannot comment on whether the observed increase in PbO_2 is beneficial to the tissues. However, this has been addressed by others [17–20] and was not the aim of this study. Sixth, the duration of induced hyperoxia was 15 min; therefore, we cannot comment on the physiological effects of longer term changes in PbO_2, potential adverse consequences of longer exposure to normobaric hyperoxia, or patient benefits. Seventh, there were relatively few tests performed when PbO_2 was low (PbO_2 was <10 mmHg in only one test). Since the PbO_2 response to a FiO_2 increase depends in part on the baseline PbO_2 it is conceivable that whether PbO_2 is compromised or not also may influence the results; this will require further study. Finally, the number of patients with poor outcome was relatively small; therefore, other factors related to outcome may not be apparent from these results. Despite these limitations, this is the first study to examine the effects of induced hyperoxia on PbO_2 in children with severe TBI. The study demonstrates that hyperoxia consistently increases PbO_2 but that this effect is variable, and in part is influenced by the baseline PbO_2. The location of the catheter and length of time after injury may be contributing factors.

Determinants of the PbO_2 Response

PbO_2 was significantly increased by hyperoxia in this study; however, the PbO_2 response relative to the change in PaO_2 ($\Delta PbO_2/\Delta PaO_2$) challenge varied widely (2–61%). The magnitude of this response, however, was related to baseline PbO_2. When baseline PbO_2 was low, the corresponding response of PbO_2 to hyperoxia was reduced. Rosenthal et al. [8, 29] demonstrated in adults an association between PbO_2 and the achieved PaO_2 with increased FiO_2, which in turn was related to lung function. They observed a significant relationship between PbO_2 and the product of CBF and cerebral arteriovenous oxygen tension difference. Even though they used a combination of global and local factors, their results suggested that PbO_2 may be more indicative of oxygen diffusion rather than simple perfusion or oxygen delivery. This is consistent with the views of Menon et al. [30] and Bullock [31] that the increased oxygen tension in the tissue may overcome diffusion barriers by increasing the pressure gradient from the capillary to the cell. It is possible that the findings of our study that oxygen reactivity was less when PbO_2 was low may be due mechanisms limiting tissue perfusion or oxygen diffusion that may be associated with low PbO_2 and may also limit the response of the tissue to increased PaO_2. This relationship between baseline PbO_2 and oxygen reactivity is consistent with findings in adult studies [32, 33].

Outcome and the PbO_2 Response to Increased FiO_2

We observed an inverse relationship between a greater $\Delta PbO_2/\Delta PaO_2$ and worse outcome. One possible explanation for this is that the regulation of local oxygen tension in the microcirculation may be altered in the more injured brain. The normal microvascular response to increased oxygen tension in the tissues is vasoconstriction [24, 34]; however, experimental stroke studies demonstrate that this phenomenon may be absent or even reversed in injured or penumbral tissue [13, 35]. A similar phenomenon also may explain different responses of PbO_2 to changes in $PaCO_2$ in injured versus noninjured tissue [36, 37]. Therefore, the increased response of PbO_2 for a given change in PaO_2 in this study may reflect an alteration of normal tissue regulatory mechanisms, which may in turn be associated with poor outcome. A similar finding was reported by Van Santbrink et al. [38] in adult TBI, in which patients with a lower O_2 reactivity had better outcomes. We also observed a greater O_2 reactivity in PbO_2 catheters located in a pericontusional location, which may be consistent with the above theory. However, in this study a reduced response of PbO_2 to an FiO_2 increase was also associated with low baseline PbO_2, and in pediatric and adult TBI low PbO_2 has been reported to be associated with poor outcome [1, 4, 6, 39]. Hlatky et al. [32] found that patients with apparent ischemia had the lowest response to hyperoxia, suggesting that a poor response to hyperoxia would be associated with poor outcome. It is possible that both robust and poor PbO_2 responses to hyperoxia may be associated with poor outcome, but are measures of different processes. Our data do not allow us to clarify this issue. Nevertheless our findings and those of others suggest that the PbO_2 response to a "treatment" may be just as important to outcome as the threshold of PbO_2 that indicates brain hypoxia.

Is There a Role for Normobaric Hyperoxia in TBI?

Our study shows that hyperoxia of short duration (15 min) can increase PbO_2. Whether this improves brain metabolism or can benefit a child with severe TBI is not addressed by our study. The role of hyperoxia after TBI is unknown and subject to much debate. Furthermore

hyperoxia, particularly when of long duration (>24 h), has several well-described potential deleterious effects on the lungs, brain, and cerebral blood vessels [40]. However, short periods of hyperoxia do not appear to increase oxidative stress [41, 42] and short-term exposure (<24 h) to normobaric hyperoxia is probably well tolerated with few adverse effects [35]. The side-effects, e.g., vasoconstriction, may not always mean "worse" since vasoconstriction in the brain may alleviate increased ICP or divert blood flow from "normal" to "impaired" tissue. Experimental studies have shown *improved* CBF and oxygenated Hb in ischemic core and penumbral tissue [35]. Different microvasculature responses to increased oxygen tension and a reduction in metabolic burden due to decreased peri-infarct depolarization may in part explain these findings.

Several clinical studies in adult patients with TBI have attempted to define the effect of normobaric hyperoxia on brain tissue metabolism, but the results have been conflicting [17–20, 43, 44]. It may be that the effect of hyperoxia depends in part on the nature of the ischemic insult. For example, in rats with ischemia induced by MCA occlusion, hyperoxia reduced infarct size and improved outcome [35, 45] while in dogs worse outcome was observed with hyperoxia after cardiac arrest [46]. Although hyperoxia increases tissue oxygen tension, it may not improve oxygen delivery to the brain, particularly under conditions of brain ischemia [47]. On the other hand, increased oxygen tension in the tissues may improve mitochondrial function in ways not yet fully understood [31, 48], such as an increased O_2 pressure gradient which overcomes diffusion-limited tissue hypoxia [30] and the preferential use of dissolved oxygen for tissue oxygenation [49, 50]. It is our opinion that hyperoxia may have a role in TBI as a means to test PbO_2 monitor function or as part of a cause-directed and stepwise approach to treatment for compromised PbO_2 provided the response to the altered FiO_2 can be measured. Whether this benefits the patient, and which methods of correcting PbO_2 are best, will require further study.

Conclusion

Normobaric hyperoxia significantly increases PbO_2 in children with severe TBI. There was a wide range in the PbO_2 response to increased PaO_2. The magnitude of the $\Delta PbO_2/\Delta PaO_2$ response was significantly related only to baseline PbO_2. Patients with a poor outcome had a greater PbO_2 response to a PaO_2 challenge, as did patients in whom the PbO_2 catheter was in a pericontusional location, which may reflect disturbances of local circulatory responses to changes in PaO_2.

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