Minimal PaO₂ threshold after traumatic brain injury and clinical utility of a novel brain oxygenation ratio

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OBJECTIVE Avoiding decreases in brain tissue oxygenation (PbtO₂) after traumatic brain injury (TBI) is important. How best to adjust PbtO₂ remains unclear. The authors investigated the association between partial pressure of oxygen (PaO₂) and PbtO₂ to determine the minimal PaO₂ required to maintain PbtO₂ above the hypoxic threshold (> 20 mm Hg), accounting for other determinants of PbtO₂ and repeated measurements in the same patient. They also explored the clinical utility of a novel concept, the brain oxygenation ratio (BOx ratio = PbtO₂/PaO₂) to detect overtreatment with the fraction of inspired oxygen (FiO₂).

METHODS A retrospective cohort study at an academic level 1 trauma center included 38 TBI patients who required the insertion of a monitor to measure PbtO₂. Various determinants of PbtO₂ were collected simultaneously whenever a routine arterial blood gas was drawn. A PbtO₂/PaO₂ ratio was calculated for each blood gas and plotted over time for each patient. All patients were managed according to a standardized clinical protocol. A mixed effects model was used to account for repeated measurements in the same patient.

RESULTS A total of 1006 data points were collected. The lowest mean PaO₂ observed to maintain PbtO₂ above the ischemic threshold was 94 mm Hg. Only PaO₂ and cerebral perfusion pressure were predictive of PbtO₂ in multivariate analysis. The PbtO₂/PaO₂ ratio was below 0.15 in 41.7% of all measures and normal PbtO₂ values present despite an abnormal ratio in 27.1% of measurements.

CONCLUSIONS The authors' results suggest that the minimal PaO₂ target to ensure adequate cerebral oxygenation during the first few days after TBI should be higher than that suggested in the Brain Trauma Foundation guidelines. The use of a PbtO₂/PaO₂ ratio (BOx ratio) may be clinically useful and identifies abnormal O₂ delivery mechanisms (cerebral blood flow, diffusion, and cerebral metabolic rate of oxygen) despite normal PbtO₂.

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KEYWORDS traumatic brain injury; oxygen; disease management; intracranial pressure; multimodal treatment

MULTIMODAL approaches to the management of traumatic brain injury (TBI) patients, including cerebral brain tissue oxygenation (PbtO₂), is supported by consensus statements.²¹ Cerebral hypoxia is thought to represent a better prognostic indicator than intracranial pressure (ICP) and cerebral perfusion pressure (CPP).^{25,28} The number, duration, and intensity of these hypoxic episodes (ischemic burden) have been associated

with poor prognosis.^{4,38–40} Several studies have suggested a beneficial effect of various PbtO₂-based management strategies on mortality and functional outcome, including the recently published BOOST-2 (Brain Oxygen Optimization in Severe TBI phase II) trial.^{1,23,25,26,29} Since PbtO₂ represents the oxygen content in the cerebral interstitium, it is the result of a balance between oxygen delivery (dependent on the lungs, cerebral blood flow [CBF], and diffusion

ABBREVIATIONS BOx ratio = PbtO₂/PaO₂ ratio; BTF = Brain Trauma Foundation; CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate of oxygen; CPP = cerebral perfusion pressure; FiO₂ = fraction of inspired oxygen; ICP = intracranial pressure; MAP = mean arterial pressure; PaO₂ = partial pressure of oxygen; PbtO₂ = brain tissue oxygenation; PCO₂ = partial pressure of carbon dioxide; TBI = traumatic brain injury.

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FIG. 1. Determinants of PbtO₂ and various pathophysiological causes affecting them. P/F ratio = PaO₂/FiO₂ ratio, VCO₂ = carbon dioxide production; V/Q = ventilation/perfusion. As per protocol, all of these parameters are taken into account to find the cause of a low PbtO₂. **A and B:** Copyright Francis Barnard. Published with permission. **C:** Reprinted from Menon DK, Coles JP, Gupta AK, Fryer TD, Smielewski P, Chatfield DA, et al: Diffusion limited oxygen delivery following head injury. *Crit Care Med* 32:1384–1390, 2004, journals.lww.com/ccmjjournal/pages/default.aspx with permission. Figure is available in color online only.

conditions) and consumption due to the cerebral metabolic rate of oxygen (CMRO₂).³² However, the optimal strategy to correct low PbtO₂ in accordance with its multiple determinants (Fig. 1) remains incompletely understood.

The third edition of the Brain Trauma Foundation (BTF) guidelines suggests targeting PaO₂ values above 60 mm Hg,⁶ whereas the fourth edition does not suggest PaO₂ or saturation targets.⁷ Increasing the fraction of inspired oxygen (FiO₂) to improve PaO₂ and thus PbtO₂ is an attractive and simple therapeutic target. Although PaO₂ represents only a fraction of the amount of oxygen delivered to tissues, it is the only force driving diffusion of oxygen to the mitochondria once in the capillaries.¹⁵ Since diffusion conditions are the rate-limiting step of brain O₂ delivery, targeting higher PaO₂ may be necessary to maintain adequate PbtO₂,^{24,41} despite adequate CBF. As such, low levels of PbtO₂ have been associated with PaO₂ as high as 144 mm Hg, presumably because of diffusion barriers.¹⁴ Yet, the optimal PaO₂ target level after TBI remains undefined.

PbtO₂ is also influenced by CBF and CMRO₂. Increasing FiO₂ can improve PbtO₂ even in the context of reduced CBF.¹⁷ The adequacy of this therapeutic strategy remains unclear and may create secondary injuries from mechanisms other than hypoxia.⁴⁵ Also, the current literature suffers from a lack of adjustments for these other determinants and from analyses that have not taken into account repeated measurements from the same patient.

To address these issues, we studied the relationship between PbtO₂ and PaO₂ in a group of severe TBI patients.

Our primary objective was to determine the minimum PaO₂ necessary to maintain PbtO₂ above 20 mm Hg after other determinants were taken into account and optimized. We hypothesized that the PaO₂ level required for adequate delivery to the brain would be higher than what is recommended. Our second objective was to test the concept of a brain oxygenation ratio (BOx ratio = PbtO₂/PaO₂) that would assist clinicians in the management of PbtO₂ by detecting overtreatment with FiO₂.

Methods

Patient Population

We randomly selected 53 patients with severe TBI from a list of 103 patients admitted to the neurocritical care unit of the Hôpital du Sacré-Cœur de Montréal between 2013 and 2016, who required the insertion of an intraparenchymal probe to measure PbtO₂ (Licox, Integra Lifesciences). Patients with insufficient data (n = 8) to enable appropriate statistical analyses (at least 7 gas measurements per patient) or with malpositioned probes (n = 7) were excluded. A total of 38 patients were included in the final analysis. Approval for the study was obtained from the local ethics committee.

Probes were inserted according to usual indications for ICP monitoring. Probes could be inserted in patients with an initial Glasgow Coma Scale score higher than 8 if their condition deteriorated and warranted monitoring. The insertion technique was done according to the manufac-

turer's recommendation. Adequate positioning was confirmed by CT scanning and/or by a hyperoxia test. Probes were inserted in normal-appearing white matter. Probes within 1 cm of a contusion or edema were considered malpositioned. If the patient underwent a craniectomy, the monitors were tunneled on the same side. Data from the first 2 hours postinsertion were discarded in order to allow for catheter equilibration.

Clinical Management

Mean arterial pressure (MAP) was measured from an arterial line calibrated at the foramen of Monro. CPP was calculated from measured parameters ($CPP = MAP - ICP$). All patients were managed by intensivists referring to algorithms approved by the institution to standardize care according to the BTF guidelines.⁶ The algorithms ensure brain homeostasis and adequate CPP, and prevent ICP elevation and cerebral hypoxia (Table 1). Bifrontal craniectomy was not performed in any patient, and no patient was placed in a barbiturate coma.

Data Collection

We collected demographic data at admission. Thereafter, PbO_2 and PaO_2 were collected simultaneously each time an arterial blood gas was drawn. The following determinants of PbO_2 were collected at the same time: body temperature, ICP, MAP, CPP, FiO_2 , PCO_2 , and hemoglobin. We calculated the PbO_2/PaO_2 ratio (BOx ratio) for each blood gas. Causes of low PbO_2 and the treatment used to correct it were extracted from the medical record.

BOx Ratio: PbO_2/PaO_2

Considering that most protocols aim for $PbO_2 > 20$ mm Hg and that hyperoxia can be defined as a PaO_2 above 130 mm Hg,¹⁹ we considered a cutoff ratio of 0.15 ($20/130 = 0.15$) to be a threshold of significance. This PaO_2 value, although higher than that suggested in the guidelines, seems appropriate to compensate for the diffusion barrier in the brain parenchyma. Higher PaO_2 values could be regarded as too high and compensatory for other deficient delivery mechanisms, e.g., inadequate CPP or elevated $CMRO_2$. We plotted the ratio over time for each patient and categorized the pattern of temporal evolution according to visual inspection of the graphs. Temporal evolution was categorized using a cutoff of 0.15 into 4 patterns: type A pattern with a normal ratio over time; type B with a ratio initially abnormal but increasing to normal over time; type C with an oscillatory ratio fluctuating above and below 0.15; and type D with a ratio declining over time to remain abnormal until the end of the monitoring period.

Statistical Analysis

The following limits were used to control for the influence of some extreme values: CPP 0–120 mm Hg, PbO_2 0–120 mm Hg, and PCO_2 below 80 mm Hg. Outliers were discarded. Continuous variables are summarized as means and standard deviations or medians and range, as appropriate. Categorical variables are presented as frequencies and percentages. The mean PaO_2 of each patient's data points was calculated. The relationship between PaO_2 and

TABLE 1. Summary of standardized management algorithms set forth in the BTF guidelines⁶

Management	Comment
Maintain brain homeostasis	
Aim for euvolemia	Fluid boluses or furosemide
Normoglycemia	Blood glucose 8–10 mmol/L
Normal natremia	Blood sodium 140–145 mmol/L
Normal temperature	Rectal temperature $<38^{\circ}\text{C}$
Normocapnia	PCO_2 35–40 mm Hg
Optimize CPP	See below
Prophylactic anticonvulsants	For the first 7 days
ICP management	Aim for <20 mmHg
Head of bed elevation: position for unobstructed jugular venous return	
Titration of sedation & analgesia	
Avoid hypoventilation	Correct elevated PCO_2
Neuromuscular paralysis as necessary	
Surgical evacuation of mass lesion	
CSF drainage	
Osmotherapy according to patient fluid status	Hypervolemia: mannitol 20% every 6 hrs as needed; hypovolemia: 3% NaCl every 6 hrs as needed
Therapeutic hypothermia	IV cooling catheter w/ temperature feedback
Decompressive craniectomy	
CPP management	Aim for lowest effective CPP
Initial target	>60 mm Hg
Evaluation of autoregulation	Manipulation MAP impacts on ICP ³³
Preserved autoregulation	Tolerate higher CPP according to Rosner's vasodilatory cascade theory ³⁴
Impaired autoregulation	Aim for lower CPP (minimum 50 mm Hg) according to a modified Lund therapy ²⁷
Use PbO_2 to guide target	See below; tolerated lower CPP if $PbO_2 >20$ mm Hg
PbO_2 management	Aim for >20 mmHg
Stepwise approach to cause of low PbO_2	See Fig. 1
Elevated ICP	See ICP management above
Preserved autoregulation	Trial of CPP augmentation; trial of cardiac index augmentation
Correction of diffusion barrier	Correct hypervolemia w/ furosemide
Avoid hyperventilation	Measure blood gas to ensure normal PCO_2
Minimize $CMRO_2$	Sedation & analgesia; correction of hyperthermia; continuous EEG to rule out seizures
Last resort: increase PaO_2	Increase FiO_2 or PEEP

EEG = electroencephalography; PEEP = positive end-expiratory pressure.

FIG. 2. Mean PaO₂ and PbtO₂ values of each patient during their ICU stay. The minimum PaO₂ required to maintain PbtO₂ above 20 mm Hg (all other determinants considered) in our cohort was 94 mm Hg. The horizontal dotted line represents a PbtO₂ threshold of 20 mm Hg. Three patients with a hypoxic mean PbtO₂ had a low mean CPP < 50 mm Hg due to withdrawal of life-sustaining therapy. Measurements were continued while waiting for diagnosis of brain death. Error bars indicate SD. Figure is available in color online only.

PbtO₂ was assessed using a mixed effects model to take into account multiple measurements in the same patient. To evaluate the nonlinearity of the associations between PbtO₂ and PaO₂, a quadratic term was included in a first model but was nonsignificant. Possible modifying effects of other determinants on the linear relation between PbtO₂ and PaO₂ were tested. Since the mixed effects model did not show any significant modifying effect of any determinant on the relationship between PaO₂ and PbtO₂, the mixed model was adjusted to assess the impact of PaO₂, CPP, ICP, hemoglobin, PCO₂, and temperature on PbtO₂ with a forward selection of determinants in the multivariate analysis.

We categorized patients according to a PbtO₂ threshold of 20 mm Hg and a ratio of 0.15, creating 4 categories of measurements: low PbtO₂–low ratio, low PbtO₂–normal ratio, normal PbtO₂–low ratio, and normal PbtO₂–normal ratio. The difference between categories in terms of mean CPP, ICP, PaO₂, FiO₂, temperature, hemoglobin, and ratio were tested using a mixed model followed by, in case of significant results, Kramer-Tukey contrasts. A significance level of $p < 0.05$ was used for all analyses. An independent statistician performed all analyses using SAS (version 9.4, SAS Institute).

Results

Patient Characteristics

Thirty-eight patients were included in the study. The

majority were men (68%) and the mean age was 44.5 ± 20 years. The most common causes of trauma were falls (32%) and motor vehicle accidents (30%), followed by other (21%), pedestrian versus vehicle (13%), and bicycle accidents (5%). The median initial Glasgow Coma Scale score was 4 (range 3–15). The mean ICU stay was 11.9 ± 7.4 days. The PbtO₂ monitor was in place for a mean of 6.3 ± 3.8 days, and insertion generally occurred early (day 1, $n = 16$; day 2, $n = 19$; day 3, $n = 2$; and day 6, $n = 1$). It should be noted that since it was not always possible to determine the precise time of the accident or insertion of the probe, we used the dates to determine the day of insertion. It is thus possible that insertion on day 2 might have occurred during the first 24 hours after injury. Either primary or rescue craniectomy was performed in 19 patients (50%). The mortality rate in our patient population was 45% ($n = 17$).

Relationship Between PaO₂ and PbtO₂

Each patient had a mean of 26 ± 19 data points for a total of 1006 data points. A relationship, though clinically weak, was found between PaO₂ and PbtO₂ in the mixed effects model ($b = 0.022$, $p < 0.0001$). The average PbtO₂ as a function of average PaO₂ for each patient individually is illustrated in Fig. 2. This mean PaO₂ was between 94 and 401 mm Hg (median 149 mm Hg) with the corresponding mean PbtO₂ ranging from 7 to 42 mm Hg (mean 26 ± 7 mm Hg). Three patients had mean PbtO₂ values in the hypoxic range (7, 10, and 15 mm Hg), which was due to low mean CPP < 50 mm Hg while awaiting brain death.

TABLE 2. Multivariate analysis of predictor of PbtO₂

Effect	Estimation	SE	T Test Value	p Value
Intercept	-16.9758	15.4133	-1.10	0.2778
CPP	0.1789	0.02676	6.68	<0.0001
ICP	0.1196	0.06142	1.95	0.0518
PCO ₂	0.1102	0.06233	1.77	0.0774
Temp	0.4218	0.3883	1.09	0.2776
Hemoglobin	0.03962	0.02655	1.49	0.1359
PaO ₂	0.03548	0.00571	6.21	<0.0001

SE = standard error; temp = temperature.
Mixed effects model.

PbtO₂ fell under the hypoxic threshold (20 mm Hg) in 17.8% of all our data points; only 7 patients did not have a measurement in the hypoxic range during monitoring. In these hypoxic measurements, the mean PbtO₂ value was 14 ± 6 mm Hg with an associated mean PaO₂ of 216 ± 118 mm Hg. For normal measurements, the mean PbtO₂ was 29 ± 7 mm Hg and was associated with a lower mean PaO₂ of 170 ± 78 mm Hg (not significant). CPP value (66 ± 16 mm Hg vs 73 ± 11 mm Hg), FiO₂ ($69\% \pm 25\%$ vs $53\% \pm 21\%$), and PbtO₂/PaO₂ ratio (8.7 ± 5.8 vs 20.5 ± 9.9) significantly differed between hypoxic and normal PbtO₂ measurements, respectively ($p < 0.05$ for all comparisons).

No determinants of PbtO₂ (ICP, CPP, MAP, PCO₂, hemoglobin, or temperature) modified the relationship be-

tween PaO₂ and PbtO₂. In multivariate analysis, only PaO₂ and CPP were predictive of PbtO₂ ($p < 0.001$, Table 2).

PbtO₂/PaO₂ Ratio

Figure 3 summarizes the relationship between PbtO₂ and PbtO₂/PaO₂ (the BOx ratio). The ratio was low in 41.7% of all measurements. Despite a low ratio, PbtO₂ values were normal in 27.1% of measurements and associated with a mean PaO₂ of 250 ± 71 mm Hg (yellow category). Patients with measurements within the low PbtO₂-low ratio category (14.6% of measurements) had significantly lower CPP than those with normal PbtO₂ (red, 64 mm Hg; yellow, 72 mm Hg; and orange and green, 74 mm Hg; $p < 0.001$). Within this category, various causes of low PbtO₂ were reported by the attending physician, including hypocapnia, low CPP, low cardiac index, hypervolemia, cerebral edema, and long equilibration time. Patients with an abnormal ratio (red and yellow categories) had higher mean PaO₂ (yellow, 250 mm Hg; red, 242 mm Hg) than patients with a normal ratio (green, 130 mm Hg; orange, 98 mm Hg; not significant). Patients with a low PbtO₂ and a normal ratio (orange, 3% of measures) had the lowest mean PaO₂ (98 mm Hg). FiO₂ was also significantly different between categories except between those with a normal ratio ($p < 0.0001$).

Figure 4 shows typical examples of the 4 patterns of temporal evolution of the PbtO₂/PaO₂ ratio: type A ($n = 7$), type B ($n = 6$), type C ($n = 15$), and type D ($n = 10$). The mortality rate for each type of pattern was 8.5% for type

BOx ratio: PbtO ₂ /PaO ₂				
PbtO ₂		< 0.15	≥ 0.15	n
	≥ 20	n = 273 (27.1%) Mean ratio = 0.11 ÷ Mean CPP = 72 Mean ICP = 11 Mean PaO ₂ = 250 Mean FiO ₂ = 70% †	n = 554 (55.1%) Mean ratio = 0.25 ÷ Mean CPP = 74 Mean ICP = 14 Mean PaO ₂ = 130 Mean FiO ₂ = 45% †	827 (82.2%)
	< 20	n = 147 (14.6%) Mean ratio = 0.06 ÷ Mean CPP = 64 * Mean ICP = 17 * Mean PaO ₂ = 242 Mean FiO ₂ = 74 % †	n = 32 (3.2%) Mean ratio = 0.19 ÷ Mean CPP = 74 Mean ICP = 11 Mean PaO ₂ = 98 Mean FiO ₂ = 51% †	179 (17.8%)
	n	420 (41.7%)	586 (58.3%)	1006

FIG. 3. Categorization of patients according to PbtO₂ and the BOx ratio. ± All mean ratios are significantly different for each category ($p < 0.0001$). * Mean CPP and ICP are significantly different from the other groups ($p < 0.0008$). † All mean FiO₂ values are different between each category except between orange and green ($p < 0.0001$). Potential interpretations (see PbtO₂/PaO₂ Ratio in Discussion): the green box represents a normal condition. The orange box might represent a situation in which lung function is altered. The yellow box might represent a situation in which diffusion is severely impaired or optimal CPP targets are unusually high. The red box represents a critical situation where many mechanisms of O₂ delivery are impaired. Figure is available in color online only.

FIG. 4. Representative examples of patterns of evolution over time according to the BOx ratio ($\text{PbtO}_2/\text{PaO}_2$) in 4 patients. The graphs show 4 distinct patterns identified in the cohort. Type A ($n = 7$): the ratio is above 0.15 throughout the monitoring period (A); type B ($n = 6$): the ratio is increasing over time (B); type C ($n = 15$): the ratio is fluctuating rapidly and appears to oscillate (C); and type D ($n = 10$): the ratio is continuously below 0.15 and/or is decreasing over time (D). The ratio was calculated at each arterial blood gas measurement. Mortality was not statistically different between groups. Craniectomy was performed in $n = 2$ (29%) of type A, $n = 4$ (67%) of type B, $n = 8$ (53%) of type C, and $n = 5$ (50%) of type D patterns. Note that PbtO_2 can be normal despite a low ratio (see text). Figure is available in color online only.

A, 33.3% for type B, 46.7% for type C, and 60% for type D (not significant).

Discussion

Our study shows that PaO_2 level set with FiO_2 titration is a major independent determinant of PbtO_2 , and the use of the BOx ratio ($\text{PbtO}_2/\text{PaO}_2$) can alert the clinician about FiO_2 overtreatment and other causes of impaired O_2 delivery.

Minimal PaO_2 Required to Prevent Cerebral Hypoxia

The minimum PaO_2 required to maintain PbtO_2 above 20 mm Hg in our sample population was 94 mm Hg. This is well above the recommended value of the BTF guidelines (60 mm Hg) and was required, despite the fact that other determinants of PbtO_2 were optimized⁶ according to our protocol (Table 1). This finding suggests that higher PaO_2 should be targeted during the first few days after injury and that clinicians cannot rely solely on the pulse oximeter, since it only shows desaturation < 90% when PaO_2 reaches

a critical value of 60 mm Hg. This might translate into an important therapeutic implication even for physicians not using a PbtO_2 probe if conveyed in guidelines. It should be noted that PaO_2 required to maintain PbtO_2 above the hypoxic threshold may be higher than 94 mm Hg and this value only represents the minimum in our population.

Our finding is supported by previous literature. An altered diffusion of oxygen across the blood-brain barrier probably explains this higher PaO_2 requirement.²⁴ Since PaO_2 is the driving force of diffusion, increasing diffusion distance from the capillary to the neuron will diminish delivery of oxygen.¹⁵ This concept is challenging for critical care specialists who rely mainly on pulse oximeters to evaluate the amount of oxygen delivered to organs. Although saturation of hemoglobin is the major determinant of total blood oxygen content, it is not involved in the diffusion process.¹⁵ A recent [^{18}F]FMISO ([^{18}F]fluoromisonidazole) PET study showed the presence of hypoxic neurons after TBI, even in the absence of classic macrovascular ischemia, and concluded that diffusion barriers in the form of microvascular ischemia or edema were responsible for

this finding.⁴¹ This does not diminish the importance of maintaining adequate CPP, an important determinant of PbtO₂ as shown in the multivariate analysis, but rather adds to the understanding of cerebral physiology and potential therapeutic targets.

The fact that we accounted for repeated measures in the same patient is a major strength of our statistical analysis of the relationship between PaO₂ and PbtO₂. To the best of our knowledge, no study has used such analysis in the past, and although a linear association was found between PaO₂ and PbtO₂, it is weak from a clinical perspective ($b = 0.02$, $p < 0.0001$). Although increasing PaO₂ may correct PbtO₂, the magnitude of this correction may be limited by CBF,¹⁷ weakening the association between PbtO₂ and PaO₂, as shown in the multiple regression analysis. This weak association might also be explained by the fact that PaO₂ was sometimes used to correct for abnormal oxygen delivery mechanisms (e.g., decreased CPP) as supported by the PbtO₂/PaO₂ ratio approach.

Brain Oxygenation Ratio: PbtO₂/PaO₂

The concept underlying the use of this ratio is based on the fact that, in normal conditions, most of the oxygen present in the blood should be measured in the brain interstitium considering CBF and diffusion are normal and that CMRO₂ is adequately coupled with CBF. Under these conditions, only an increase in oxygen diffusion distance from the capillary to the neuron would require increasing PaO₂ to maintain normal PbtO₂.^{24,41} Since it is possible to compensate for a decrease in PbtO₂ due to low CBF by increasing PaO₂,¹⁷ this Band-Aid approach to the management of PbtO₂ will mask a decrease in CBF but will be associated with a decreased PbtO₂/PaO₂ ratio. While increasing PaO₂ prevents hypoxia when there is a lack of CBF,³⁷ this therapeutic strategy is not supported by evidence.¹⁰ In addition, CBF regulates other brain homeostatic mechanisms apart from oxygen delivery.⁴⁵ Hyperoxia is also known to induce cerebral vasoconstriction^{13,30} and potentially increase free radical production³¹ and has been associated with worse outcome in other brain ischemic injuries.^{12,20,42,44} Vasoconstriction independent from a decrease in PCO₂ is associated with increases in PaO₂ and causes CBF to decrease by as much as 33% as determined by the spin labeling MRI technique.¹³ Additionally, physiological events after exposure to higher PaO₂ lead to increased brain tissue PCO₂, which in turn leads to hyperventilation and a decrease in PCO₂, leading to further vasoconstriction.¹³ Direct oxygen toxicity to neurons may occur through oxygen free radicals but can also be mediated through activation of persistent inflammation and activation of the macroglia.¹⁶ Furthermore, a dose-dependent relationship with outcomes supports the biological plausibility of toxic oxygen levels.^{20,44} A recently published study suggested that PaO₂ above 150 mm Hg for more than 6 hours after cardiac arrest is associated with worst functional outcomes.⁴⁴ Although anoxic brain injury and TBI have different pathophysiologies, this finding warrants caution when using elevated FiO₂ to treat TBI patients. Finally, a meta-analysis evaluating supplemental oxygen therapy in acutely ill patients suggested an increased mortality associated with hyperoxia, although this association is less clear in patients with neurological

conditions.⁸ All of these findings highlight the fact that simply increasing PaO₂ to improve PbtO₂ is not a straightforward therapy and should be undertaken with caution as it might decrease CBF and have metabolic repercussions. Thus, a low BOx ratio could alert the physician that cerebral physiology is not optimized despite normal PbtO₂.

The ratio was below our predetermined threshold in a substantial proportion of our 1006 measurements (41.7%). A low ratio (< 0.15) was observed despite normal PbtO₂ values being recorded at the bedside 27.1% of the time. This was because FiO₂ was increased to compensate for marginal PbtO₂ values despite normal CPP. Consequently, the mean PaO₂ observed in the normal PbtO₂-low ratio (yellow) category of patients was very high (250 mm Hg). This potentially represents situations in which diffusion is markedly affected or CBF should be optimized. A high PaO₂ was also observed in the red category (low PbtO₂-low ratio) but was associated with a significant difference in mean CPP between hypoxic and nonhypoxic PbtO₂ (64 mm Hg vs 74 mm Hg), suggesting that PaO₂ incompletely counteracts a low CBF. Consistent with these observations, clinicians identified various causes of low CBF and an increased diffusion barrier in patients with a low ratio. Based on clinical observations and physiological reasoning,¹⁹ we consider that increasing PaO₂ above 130 mm Hg to correct PbtO₂ requires a careful evaluation of all the possible causes of decreased cerebral oxygenation (Fig. 1) to avoid overtreatment with FiO₂.

Since PaO₂ and PbtO₂ are closely related, the ratio offers the possibility of trending their relation over time, much the same way the PaO₂/FiO₂ ratio allows in acute respiratory distress syndrome.² Temporal patterns illustrate the clinical utility of the ratio and may be related to mortality in our population. Patients with a type A pattern of temporal evolution would have a relatively normal physiology and no major diffusion barrier. Patients with a type B pattern could present with insufficient O₂ delivery or increased consumption that improves over time. The patient illustrated in Fig. 4B showed signs of O₂ diffusion problems related to the insertion of the probe, then a decrease in cardiac index and relatively low CPP (60 mm Hg) that were corrected with higher CPP targets (> 70 mm Hg). This pattern was also associated with the highest rate of craniectomy. Later, hyperemia developed due to sepsis (high PbtO₂ and ratio). These observations are consistent with those in studies demonstrating decreased CBF early after injury where higher CPP targets may be required with subsequent hyperemia^{5,22} and with studies optimizing CPP according to the pressure reactivity index.^{3,9,11,18,36} Type C patterns demonstrate episodes of reversible changes in brain physiology and imply the occurrence of secondary insults adding up over time described in the literature as a cumulative ischemic dose (ischemic burden).^{28,35,39,40,43} Finally, in type D patterns, the patients developed sustained and persistent problems of O₂ delivery that could not be reversed. Evolution toward brain death in some patients allowed us to confirm the expected response of the ratio with increasing ICP and decreasing CPP.

Limitations

The most important limitation is the retrospective na-

ture of our study. The small sample size in terms of patients prevented us from drawing definitive conclusions about the relationship between the ratio patterns and death. Although patient care was based on a protocol, we cannot exclude that other determinants of PbtO_2 could have influenced our results regarding the minimal PaO_2 required to maintain cerebral oxygenation. This effect was minimized since a blood gas was drawn only after ICP, CPP, or CMRO_2 were addressed as potential causes of cerebral hypoxia.

We could not statistically determine a specific threshold for the proposed ratio because it is not amendable to a receiver operating characteristic curve analysis since we could not compare the ratio with a clinically measurable gold standard (CBF or diffusion barrier). Our suggested threshold would be best tested in a multimodality monitoring setup incorporating CBF, diffusion, and metabolism measurements along with PbtO_2 . CT perfusion was not available in our center at the time the study was conducted. Increasing PaO_2 as a one-size-fits-all approach to correct PbtO_2 could also be tested in this setup. Further studies are necessary to define the implications of the $\text{PbtO}_2/\text{PaO}_2$ ratio and therapeutic strategies correcting PbtO_2 .

Conclusions

Our results suggest that PaO_2 should be maintained above the BTF recommendation in order to ensure adequate cerebral oxygenation while oxygen diffusion barriers resolve. Second, a brain oxygenation ratio (BOx ratio) below 0.15 allows the clinician to recognize altered cerebral physiology despite normal PbtO_2 . It might help clinicians recognize when FiO_2 has been used to correct for altered CBF-, diffusion-, or CMRO_2 -related issues.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Bernard, Dellazizzo. Acquisition of data: Bernard, Dellazizzo, Demers, Williams. Analysis and interpretation of data: Bernard, Demers, Charbonney, Serri, Albert, Williamson. Drafting the article: Bernard, Dellazizzo, Williamson. Critically revising the article: all authors. Reviewed submitted version of manuscript: Bernard, Dellazizzo, Demers, Williams, Serri, Albert, Giguère, Laroche, Williamson. Approved the final version of the manuscript on behalf of all authors: Bernard, Bernard, Williamson. Administrative/technical/material support: Williams. Study supervision: Bernard.

Supplemental Information

Previous Presentations

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