Hyperoxia in pediatric severe traumatic brain injury (TBI): a comparison of patient classification by cutoff versus cumulative (area-under-the-curve) analysis

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ABSTRACT

Objective: Hyperoxia is associated with adverse outcome in severe traumatic brain injury (TBI). This study explored differences in patient classification of oxygen exposure by PaO_2 cutoff and cumulative area-under-the-curve (AUC) analysis.

Methods: Retrospective, explorative study including children (<18 years) with accidental severe TBI (2002–2015). Oxygen exposure analysis used three PaO_2 cutoff values and four PaO_2 AUC categories during the first 24 hours of Pediatric Intensive Care Unit (PICU) admission.

Results: Seventy-one patients were included (median age 8.9 years [IQR 4.6–12.9]), mortality 18.3% (n = 13). Patient hyperoxia classification differed depending on PaO_2 cutoff vs AUC analysis: 52% vs. 26%, respectively, were classified in the highest hyperoxia category. Eleven patients (17%) classified as 'intermediate oxygen exposure' based on cumulative PaO_2 analysis whereby they did not exceed the 200 mmHg PaO2 cutoff threshold. Patient classification variability was reflected by Pearson correlation coefficient of 0.40 (*p*-value 0.001).

Conclusions: Hyperoxia classification in pediatric severe TBI during the first 24 hours of PICU admission differed depending on PaO_2 cutoff or cumulative AUC analysis. We consider PaO_2 cumulative (AUC) better approximates (patho-)physiological circumstances due to its time- and dose-dependent approach. Prospective studies exploring the association between *cumulative* PaO_2, physiological parameters (e.g. ICP, $PbtO_2$) and outcome are warranted as different patient classifications of oxygen exposure influences how its relationship to outcome is interpreted.

Introduction

It is well known that hypoxemia is associated with worse outcome in TBI (1–4). The influence of hyperoxia on outcome remains controversial. Suggested mechanisms of potential negative effects include cerebral vasoconstriction in a similar manner as hypocarbia, oxidative stress and inflammation (2,5–7).

Most studies investigating hyperoxia and outcome in TBI and other patient groups used (arbitrary) cutoff values for hyperoxia such as 200, 250 or 300 mmHg, respectively (2,8–11). Whether the analysis of different cutoff values adequately approximates oxygen exposure is questionable due to the multifactorial and dynamic nature of oxygen physiology in combination with continuous supplemental oxygen exposure in the majority of cases. A study in pediatric post-cardiopulmonary resuscitation (CPR) patients by van Zellem et al. introduced a new innovative method in defining and measuring hyperoxia and oxygen exposure: the cumulative analysis using the area-under-the-curve (AUC) PaO_2 calculation, which is a commonly used approach to estimate drug exposure in pharmacological studies (12–14). Although each method of oxygen exposure analysis has its limitations, our hypothesis is that the longitudinal, cumulative approach better addresses the (patho-)physiology of cerebral hyperoxia as it takes time- and dose-dependent factors into account (15).

The aim of our study was to compare the hyperoxia classification of pediatric severe traumatic brain injury patients during the first 24 hours of Pediatric Intensive Care Unit (PICU) admission by using conventional PaO_2 cutoff analysis and area-under-the-curve (AUC) PaO_2 cumulative analysis. The rationale being that patient classification is crucial to how we subsequently associate hyperoxia to outcome measures, such as morbidity and mortality.

Material and methods

Study design and setting

This is a retrospective observational study with exploratory aims. The study was performed at PICU of the Erasmus MC – Sophia Children's Hospital, a tertiary-care hospital providing regional pediatric health care for the southwest of The Netherlands (estimated regional population of 4.2 million inhabitants). This population is a representative sample of the Dutch population. Waiver of consent was granted by the ethical review board of the Erasmus MC due to the noninvasive matter of the study (MEC 2015–583).

Study aim

The aim of this observational study was to explore two methods of analyzing oxygen exposure (cutoff vs. cumulative AUC PaO_2) per patient. The importance of comparing these two methods is to ascertain if the type of analysis leads to differences in hyperoxia patient classification.

Subjects

All children admitted to the PICU of the Erasmus MC – Sophia Children's Hospital with severe TBI between January 2002 and July 2015 were evaluated for study eligibility. Inclusion criteria were severe TBI defined as a Glasgow Coma Scale (GCS) of eight or less requiring ICP-monitoring in the PICU and the presence of an arterial line for the acquisition of PaO_2 values. Treatment of severe TBI in our hospital conformed international guidelines for acute medical management of severe traumatic brain injury [16]. Exclusion criteria were non-accidental TBI, such as child battering and no arterial line in situ for PaO_2 sampling.

Data collection

Data were derived from ambulance registration forms, electronic medical records and our Patient Data Management System (PDMS) and collected for the first 24 hours after the event (T = 0). Due to inadequate documentation of the precise time of event in the majority of cases, this had to be approximated. Therefore, we chose to define T = 0 as the PICU admission time. This is deemed a reasonable solution because of a rapid response time of medical emergency services in our region with relatively little time between the estimated time of event (based on ambulance registration forms, ER admission forms) and PICU admission (median 1.7 hours, IQR [0.1–22.3]).

The following data were collected (1): basic patient characteristics (e.g., gender, age, PIM3 and PRISM scores) (2), TBI characteristics (e.g. etiology, first recorded GCS (at the scene or, if unknown, GCS at the Emergency Room) and radiological findings), 3) outcome (mortality during PICU admission), 4) laboratory values (Arterial Blood Gas (ABG): arterial pH, lactate, PaO_2, $PaCO_2$) and 5) values of ICP, Fraction of inspired Oxygen (FiO_2) and Mean Airway pressure (MAP). The Oxygenation Index (OI) was calculated as follows: (FiO_2 x MAP)/PaO_2.

Statistical analysis

Data are presented as frequencies (%), mean (standard deviation, SD) for normally distributed variables or median (interquartile range, IQR) for continuous variables that were not normally distributed. Correlation between PaO_2 max and total PaO_2 AUC in the first 24 hours of PICU admission was calculated using Person correlation coefficient (95% confidence interval). It was pre-defined that the correlation was excellent with a coefficient above 0.80, good between 0.61 and 0.80; fair to moderate when between 0.21 and 0.60; and poor when below 0.20. Univariable logistic regression was used to explore the differences in association between the two approaches to define hyperoxia and the

outcome measure 'mortality.' A two-sided p-value of ≤0.05 was considered statistically significant for all analyses. Data analysis was performed with IBM SPSS Statistics 25.0.0 (IBM Inc.) and GraphPad Prism 8.30 for Windows (Graph-pad Software, Inc.).

Oxygen exposure analysis

The presence of hyperoxia during the first 24 hours of PICU admission was investigated using two different methods of analyzing PaO_2: the traditionally used cutoff value analysis and secondly the cumulative analysis of PaO_2 using the trapezoidal method. Both methods were used in each individual patient from the cohort. Subsequently, a comparison was made on how patients were categorized dependent on the type of oxygen exposure analysis (cutoff vs AUC). No correction of patient-specific variables was necessary as comparison of the type of analysis was per patient and not patient subgroups.

PaO_2 cutoff analysis: Three different cutoff values of hyperoxia (>200, >250 and >300 mmHg) were used as proposed in the literature [2,8–11]. The highest PaO_2 value for each individual patient was determined for the first 24 hours of PICU admission. Patients were categorized in 1 of these 3 cutoff groups based on which of the aforementioned cutoff values was surpassed.

PaO_2 cumulative area-under-the-curve (AUC) analysis: The AUC of PaO_2 was calculated to determine the *cumulative* PaO_2 of each patient during the first 24 hours of PICU admission. A minimum of four PaO_2 measurements within the first 24 hours was required for this analysis. The actual number of available PaO_2 samples per patient in this 24-hour time frame was dependent on how frequently an arterial blood gas was drawn for routine clinical care.

One step of the AUC calculation included a correction for the time of PaO_2 measurement for patients who did not have a 24-hour time period in which PaO_2 was measured (e.g. the patient died within 24 hours). This resulted in a cumulative PaO_2 per hour, which was converted into the cumulative PaO_2 by multiplying by 6, 18, or 24, respectively.

Exploratory analyses of cutoff and cumulative PaO_2: To enable comparison of PaO_2 AUC patient classification to PaO_2 cutoff categories, we divided AUC values into the following four groups: AUC value <2000, 2001–4000, 4001–6000 and >6000. These groups are based on evaluation of individual case analysis whereby an AUC value <2000 reflected 'physiological' oxygen exposure, an AUC value between 2000 and 4000 'intermediate' oxygen exposure and AUC values >4000 'high' oxygen exposure. The values for PaO_2 AUC and PaO_2 max are continuous and are exploratively compared in univariable regression analyses. In the literature PaO_2 max is (mostly) used in combination with cutoff values, thus creating different hyperoxia categories.

Results

Patient and TBI characteristics

Seventy-one patients met the inclusion criteria for this study between the study period of January 2002 and July 2015. The median age was 8.9 years [IQR 4.6–12.9] and 51 (72%) patients were male. The mortality rate was 18.3% (N = 13) of which seven patients (54%) died within 24 hours. The etiologies of

death were: brain death (n = 6, all of which had an apnea test), withdrawal of life-sustaining treatment (n = 6) and cardiac arrest (n = 1). The cause of the cardiac arrest was unclear and postmortem examination did not reveal a specific etiology. Withdrawal of life-sustaining treatment because of unfavorable neurological prognosis was based on repeated neurological examination, brain imaging and electroencephalography. The majority of patients had been involved in traffic accidents (53%) and displayed multiple injuries on cerebral-computed tomography (CT) scan. Table 1 displays the patient characteristics of the total study cohort.

Oxygen exposure analysis

Figure 1 visually demonstrates the difference in how oxygen exposure can be viewed when defined by a single PaO_2 cutoff value versus PaO_2 cumulative value (AUC) for the first 24 hours of five different patients in our cohort. The individual

Table 1. Overview of patient characteristics.

	N (%) or median [IQR] when applicable
Demographics (N = 71)	
Age (years)	8,9 [4,6–12,9]
Male	51 (72)
GCS (first recorded)	6 [4–8]
Pupils fixed and dilated (at presentation)	10 (14)
Etiology TBI	
Fall	24 (17)
Hit by motorvehicle	16 (18)
Passenger motorvehicle accident	21 (19)
Hit by object	10 (14)
Radiological findings (N = 71)	
Fracture	51 (72)
Subdural hematoma	26 (37)
Epidural hematoma	13 (20)
Subarachnoidal hematoma	19 (21)
Contusion	39 (55)
Diffuse axonal injury	22 (22)
Midline shift	18 (23)
Hydrocephalus	5 (7)
Surgical intervention (N = 71)	
Decompressive craniotomy	13 (20)
Extraventricular drain	3 (4)
Severity scores (N = 71)	
PIM3 probability	0.034 [0.028–0.068]
PRISM3	17 [11–22]
Arterial blood gas values (N = 62)	
Lowest pH	7.24 [7.19–7.32]
Highest lactate, mmol/L	2.7 [1.9–3.8]
Lowest PaO_2, mmHg	72 [51–90]
Highest PaO_2, mmHg	289 [202–405]
Lowest $PaCO_2$, mmHg	29 [26–31]
Highest $PaCO_2$, mmHg	46 [40–61]
Cumulative PaO_2 AUC 0–24 hrs (N = 66)	3105 [2547–4015]
Ventilator settings (max value per patient, N = 61)	
Oxygenation index	4 [2–9]
FiO_2	46 [35–78]
Mean airway pressure	11 [9–14]
ICP values (N = 70)	
Median ICP	16 [11–18]
Minimum ICP	0 [0–9]
Maximum ICP	34 [24–58]

All presented values were determined for the first 24 hour of PICU admission. AUC = area-under-the-curve, GCS = Glasgow Coma Scale, ICP = intracranial pressure, PICU = Pediatric Intensive Care Unit, PIM = Pediatric Index of Mortality, PRISM = Pediatric Risk of Mortality Score, TBI = traumatic brain injury.

patients have varying PaO_2 cumulative (AUC) values (presented as increasing values from low to high in patient A and patient E, respectively). However, this does not mean that a single, absolute PaO_2 value necessarily crosses a cutoff threshold. Examples of this difference are patients C and D who have similar cumulative (AUC) PaO_2 values (approx. 3700 each) but only patient D crosses the 300 mmHg PaO_2 threshold. This illustrates how different methods of oxygen analysis might lead to different interpretations of oxygen exposure.

Comparison of PaO_2 cutoff and PaO_2 AUC classification is represented in Table 2. This showed heterogeneity in patient classification whereby some patients could be categorized as both 'hyperoxic' and relatively physiological oxygen exposure depending on which analysis was used. Furthermore, patients classified as 'intermediate' oxygen exposure based on PaO_2 AUC cumulative analysis showed a wide distribution over the various PaO_2 cutoff values. Figure 2 illustrates the variation in patient hyperoxia classification based on the type of analysis and is underlined by a Pearson's correlation coefficient for PaO_2 max and PaO_2 cumulative AUC of 0.40 (95% CI 0.17–0.58), p-value <0.001, which reflects fair to moderate correlation.

Table 3 reflects an exploratory univariable logistic regression analysis of PaO_2 cutoff versus cumulative (AUC) and mortality. This yielded a possible association with cumulative PaO_2 during the first 24 hours of PICU admission (OR 1.059, CI 1.005–1.117), p-value 0.032. No association was found with the three PaO_2 cutoff values or the (continuous) maximum PaO_2 value.

Discussion

This study compared two different types of oxygen exposure analysis (PaO_2 cutoff versus cumulative area-under-the-curve analysis) and showed major differences in patient classification of hyperoxia and in the association between hyperoxia and mortality. This is an important finding as it could influence our understanding of the relationship between hyperoxia and outcome measures and subsequent therapeutic targets we formulate for clinical care.

The importance of improving our understanding of oxygen physiology in TBI is emphasized by the established harmful effect of hypoxia resulting in international guidelines advocating brain tissue oxygenation tension ($PbtO_2$) monitoring (3,24). However, the effects of hyperoxia remain controversial. No formal definition for hyperoxia exists and different modes of analysis have been applied leading to reports of both beneficial and adverse effects of hyperoxia in critical illness in general and TBI specifically (2,4,8,10,11,18,20,23,25–29). To further compound the complexity of this debate, there are reports that suggest the *timing* of arterial hyperoxia, at admission and during the first 24 hours, could influence outcome measures (2,21,30). Potential harmful effects of hyperoxia (e.g. oxygen toxicity due to reactive oxygen species and vasoconstriction) could be accentuated in the (severe) TBI patient due to higher susceptibility for inflammation and cardiovascular instability thus potentially contributing to increased morbidity and mortality (2,5–7).

The majority of studies on hyperoxia and TBI use a single value to describe oxygen exposure: either a PaO_2 value above
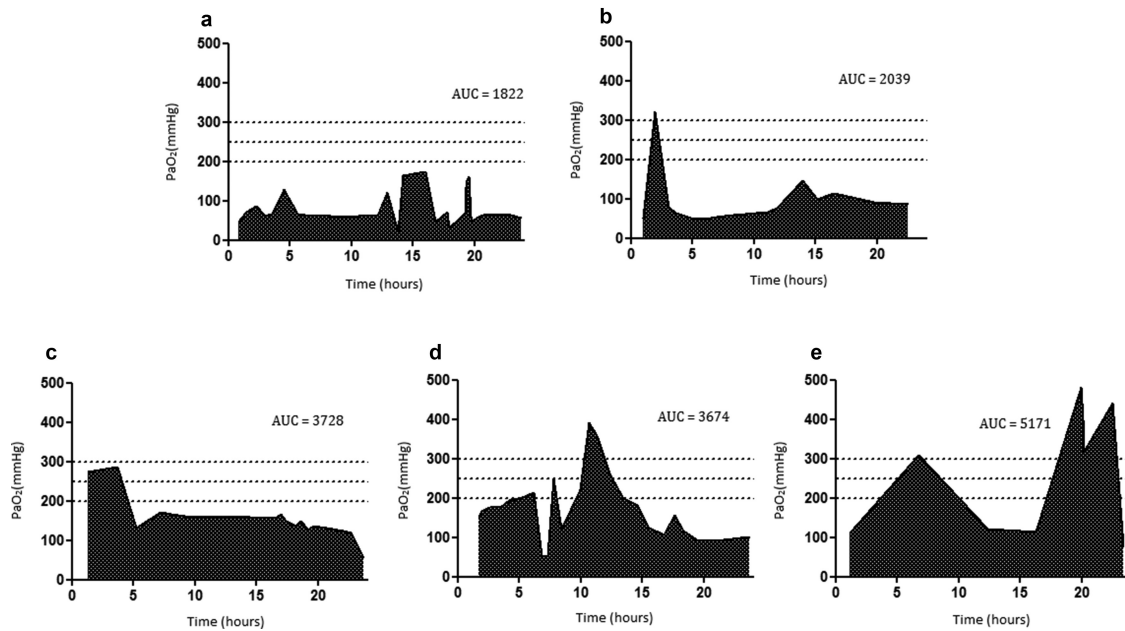
Figure 1. Oxygen exposure of five patients comparing PaO_2 cutoff versus PaO_2 cumulative analysis (area-under-the-curve, AUC). *Legend*: (A) Low AUC values, no PaO_2 above cutoff values. (B) Low AUC value, PaO_2 above cutoff values. (C) Intermediate AUC value, PaO_2 above 2 cutoff values but not highest cutoff value. (D) Intermediate AUC, PaO_2 fluctuates yet crosses all cutoff values. (E) High AUC values, PaO_2 above highest cutoff value.

Table 2. Patient classification table based on PaO_2 cutoff versus PaO_2 AUC.

	PaO_2 AUC				
	≤ 2000	2001–4000	4001–6000	≥6001	Total
PaO_2 cut off (mmHg)					
≤200	2	11	0	1	14
201–250	1	7	4	0	12
250–300	0	5	1	0	6
≥301	1	22	10	1	34
Total	4	45	15	2	66

All presented values were determined for the first 24 hours of Pediatric Intensive Care Unit admission.

AUC = area-under-the-curve.

Table 3. Univariable logistic regression analyses of cutoff vs. area-under-the-curve (cumulative) PaO_2 and mortality.

	OR	(95% CI)	p-Value [a]
Cutoff PaO_2 values			
Max. PaO_2 > 200 mmHg	1.791	(0.353–9.074)	0.482
Max. PaO_2 > 250 mmHg	2.796	(0.695–11.241)	0.148
Max. PaO_2 > 300 mmHg	1.778	(0.518–6.097)	0.360
Max PaO_2 in mmHg	1.003	(0.999–1.007)	0.171
Cumulative PaO_2 value			
AUC PaO_2 0–24 h mmHg [b]	1.059	(1.005–1.117)	0.032

AUC = area under the curve, CI = confidence interval, max. = maximum, OR = odds ratio, PaO_2 = partial pressure of arterial oxygen.

[a] two-sided *P*-value of ≤0.05 was deemed significant.

[b] Value was rescaled by dividing by 100 in advance of interpretable regression analysis.
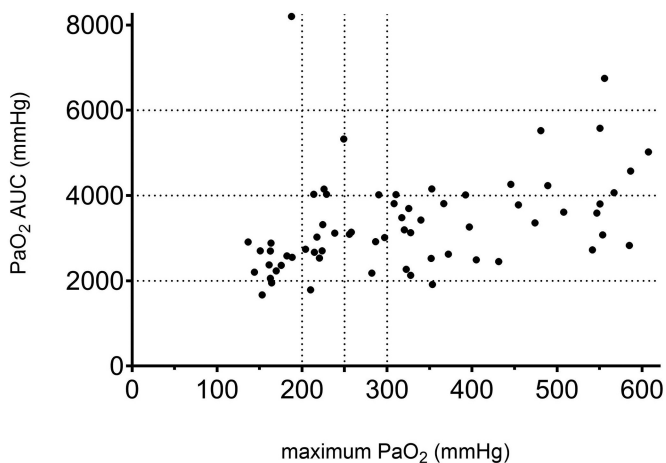
Figure 2. Correlation patient classification based on PaO_2 cutoff versus PaO_2 AUC. *Legend*: All presented values were determined for the first 24 hours of Pediatric Intensive Care Unit admission. The dotted lines represent the various hyperoxia categories. AUC = area-under-the-curve.PaO2 cutoff categories: >200, >250, and >300 mmHg respectively.PaO2 AUC categories: 2001–4000, 4001–6000, >6000, respectively. Pearson's correlation coefficient is 0.40 (95% CI 0.17–0.58), *p*-value <0.001.

an arbitrary cutoff or a maximum PaO_2 value used as a continuous value in analysis (2,4,8–11,19,20,25,26,28,31,32). However, fluctuations in PaO_2 levels are common in critical illness and TBI. The biological rationale for considering an alternative approach to oxygen exposure analysis other than cutoff methodology is that the PaO_2 cumulative (AUC) analysis incorporates time- and dose-dependent factors. This could yield a more realistic description of overall oxygen exposure in comparison to a single cutoff value. In this context, oxygen can be seen as one of the most commonly prescribed drugs in the pre-hospital, emergency room and critical care setting (22,29). This could warrant an analytic approach of its exposure similar to other pharmacological agents whereby the clinician attempts to navigate dosage between the margins of efficacy and safety, so-called 'therapeutic drug monitoring' (33). Parallels can be drawn from pharmacological studies on optimal dosing strategies for antibiotics. Comparison of cutoff versus cumulative

(AUC) methodology in this context has demonstrated that cumulative (AUC) analysis could lead to adequate exposure/efficacy for the intended purpose, often at a lower dosage than initially calculated, and subsequently with less toxicity than dosing schemes based on peak and trough levels alone (13,14). Applying the same methodology to evaluate (cumulative) oxygen exposure could improve our understanding of oxygen pathophysiology in terms of safety and efficacy (12,15,17). Therefore, we found it of interest to explore this methodology in pediatric TBI, an especially vulnerable group where improved understanding of oxygen physiology may be one of the tools to improve overall outcome.

In essence, Figure 1 illustrates the core finding of our study where oxygen exposure and subsequent hyperoxia classification depended on which analysis method was used. Patient B would be classified as 'high oxygen exposure' based on the fact that one PaO_2 value exceeded the cutoff yet the AUC-value is low. On the other hand, patients C and D both have an 'intermediate' AUC value but would be scored differently as far as potential harmful oxygen exposure is concerned when classified by cutoff values. From a clinical point of view, this might mean that supplemental oxygen therapy with PaO_2 values consistently on the upper range of what is considered normal could be as harmful as a few moments with very high values of PaO_2 and fits the pharmacological concept of a time- and dose-dependent effect of oxygen when viewing it as a drug. The visual observations represented in Figure 1 were further underlined in Table 2 where the differences in patient classification for the total cohort became apparent and demonstrated the extent of the discrepancy in patient classification based on the type of analysis. This was also reflected by a fair to moderate correlation between maximum PaO_2 and cumulative PaO_2 (Pearson's correlation coefficient of 0.40 (95% CI 0.17–0.58, p-value < 0.001) in Figure 2.

Awareness of such potentially large differences in patient classification secondary to methodology is crucial when attempting to associate oxygen exposure to clinical outcome measures. Therefore, we explored patient classification based on cutoff or cumulative PaO_2 analysis to mortality (Table 3) and interestingly the cumulative PaO_2 of the first 24 hours of PICU admission suggested an association with mortality. No conclusions can be drawn from this finding given the retrospective, small sample size. However, it is of interest given previous observations made about oxygen exposure *timing* and outcome measures (21,30,34,35).

There are various limitations that need to be addressed. Obviously, a retrospective cohort study with a relatively small patient sample size, variable PaO_2 sampling and a short time frame (first 24 hours of PICU admission) makes it impossible to establish the superiority of one method of analysis over the other. However, this cohort provided the opportunity to explore two methods of oxygen exposure analysis in a hypothesis-generating manner.

From a data collection point of view, this study has an inclusion period of 24 hours after PICU admission because of its explorative nature. This time period does not represent the full scope of TBI pathophysiology and in future studies, it would be interesting to investigate the entire PICU admission period, especially given reports on the timing of arterial hyperoxia and outcome (21,30).

When discussing limitations in the AUC method analysis, we must acknowledge that the AUC method might not be ideal in measuring PaO_2 fluctuations. The trapezoidal rule to estimate cumulative PaO_2 is commonly used in pharmacokinetic research to measure total drug exposure (12). An important assumption of calculating the AUC using this trapezoidal rule is the predictability of the measured concentrations (such as in drugs with a substantial half life time value). This is not the case for oxygen and fluctuations in PaO_2 levels are common in critical illness and TBI, resulting in no pattern or predictability in PaO_2 levels. Nonetheless, we conclude that the PaO_2 cumulative AUC method better captures exposure variability in combination with the time- and dose-dependent factors than a single PaO_2 cutoff approach. Therefore, to optimize the granularity of the cumulative PaO_2 AUC approach in future studies, we advocate standardized, frequent PaO_2 sampling. Modalities such as transcutaneous PaO_2 monitoring might be considered for this type of analysis as it would yield high-frequency, continuous PaO_2 data (36). In general, it must be noted, that systemic arterial oxygenation (PaO_2) might not be an adequate surrogate of regional cerebral oxygenation, such as $PbtO_2$. Thus, concomitant $PbtO_2$-monitoring and microdialysis would enable a better understanding in which patient's higher supplemental oxygen administration (and subsequent PaO_2 levels) might be justified, but these modalities are currently not available in most clinical settings. Therefore, guidelines for supplemental oxygen titration on the basis of PaO_2 values would be practical in the clinical context which have been defined based on consensus in the most recent management guidelines of pediatric severe TBI (16).

TBI pathophysiology is complex, multifactorial and dynamic. Our study focuses on only one element in this complex cascade of events. We suggest further prospective studies to investigate the context of cumulative PaO_2 in relationship to other physiological parameters, such as intracranial pressure (ICP) and cerebral blood flow (CBF) as well as cerebral oxygen exposure ($PbtO_2$) and cerebral metabolism (microdialysis). This could facilitate establishing which method of oxygen exposure analysis might be most appropriate to define hyperoxia and its subsequent association with clinical outcome measures.

Conclusion

Our study findings are hypothesis-generating and demonstrate that patient classification of oxygen exposure shows major differences based on the analytic method used (cutoff versus cumulative AUC). In our opinion, the cumulative PaO_2 (AUC) analysis better accounts for the time- and dose-dependent nature of supplemental oxygen therapy and deserves further exploration using large, prospective data collection to determine which method of oxygen exposure analysis might be most appropriate before attempting to establish potential causality between hyperoxia and outcome in (pediatric) TBI and the critically ill (pediatric) patient in general. Until more definite answers can be provided on the manner to analyze and interpret oxygen exposure in critically ill (pediatric) patients and titrate this appropriately to the individual patient, awareness that oxygen is the most commonly used 'drug' in the PICU,

with the potential for toxicity, should trigger more stringent titration of supplemental oxygen where possible to suggested PaO_2 values (90–100 mmHg) conform the most recent international guidelines on the management of pediatric traumatic brain injury (16).

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