neurocritical care society Neurocrit Care (2015) 22:243–250
DOI 10.1007/s12028-014-0062-0

ORIGINAL ARTICLE

Normobaric Hyperoxia is Associated with Increased Cerebral Excitotoxicity After Severe Traumatic Brain Injury

Hervé Quintard · Camille Patet · Tamarah Suys · Pedro Marques-Vidal · Mauro Oddo

Published online: 29 August 2014

Abstract
Background Normobaric oxygen therapy is frequently applied in neurocritical care, however, whether supplemental FiO_2 has beneficial cerebral effects is still controversial. We examined in patients with severe traumatic brain injury (TBI) the effect of incremental FiO_2 on cerebral excitotoxicity, quantified by cerebral microdialysis (CMD) glutamate.
Methods This was a retrospective analysis of a database of severe TBI patients monitored with CMD and brain tissue oxygen ($PbtO_2$). The relationship of FiO_2—categorized into four separate ranges (<40, 41–60, 61–80, and >80 %)—with CMD glutamate was examined using ANOVA with Tukey's post hoc test.
Results A total of 1,130 CMD samples from 36 patients—monitored for a median of 4 days—were examined. After adjusting for brain ($PbtO_2$, intracranial pressure, cerebral perfusion pressure, lactate/pyruvate ratio, Marshall CT score) and systemic ($PaCO_2$, PaO_2, hemoglobin, APACHE score) covariates, high FiO_2 was associated with a progressive increase in CMD glutamate [8.8 (95 % confidence interval 7.4–10.2) μmol/L at $FiO_2 < 40$ % vs. 12.8 (10.9–14.7) μmol/L at 41–60 % FiO_2, 19.3 (15.6–23) μmol/L at 61–80 % FiO_2, and 22.6 (16.7–28.5) μmol/L at $FiO_2 > 80$ %; multivariate-adjusted $p < 0.05$]. The threshold of FiO_2-related increase in CMD glutamate was lower for samples with normal versus low $PbtO_2 < 20$ mmHg ($FiO_2 > 40$ % vs. $FiO_2 > 60$ %). Hyperoxia ($PaO_2 > 150$ mmHg) was also associated with increased CMD glutamate (adjusted $p < 0.001$).
Conclusions Incremental normobaric FiO_2 levels were associated with increased cerebral excitotoxicity in patients with severe TBI, independent from $PbtO_2$ and other important cerebral and systemic determinants. These data suggest that supra-normal oxygen may aggravate secondary brain damage after severe TBI.

Keywords Oxygen · Hyperoxia · Brain · Traumatic brain injury · Glutamate · Cerebral microdialysis · Excitotoxicity

Introduction

Secondary cerebral hypoxia is frequent in the early phase following severe traumatic brain injury (TBI) and is an important determinant of patient outcome [1]. Monitoring of brain tissue oxygen tension ($PbtO_2$) is increasingly used for the detection and management of secondary cerebral hypoxia in patients with TBI. Retrospective studies suggest treatment of compromised $PbtO_2$ may improve outcome of TBI [2–5], although the issue is still controversial [6–8]. Therapy of compromised $PbtO_2$ consists of a multi-step interventional strategy, including increased sedation, control of concomitant-elevated intracranial pressure (ICP), cerebral perfusion pressure (CPP) augmentation, red blood cell transfusion, and optimization of mechanical ventilation, e.g., by increasing the fraction of inspired oxygen (FiO_2) [9]. Increase of FiO_2 by way of normobaric oxygen therapy is one of the most frequently employed

H. Quintard · C. Patet · T. Suys · M. Oddo (✉)
Department of Intensive Care Medicine, Neuroscience Critical Care Research Group Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, Rue du Bugnon 46, BH 08.623, 1011 Lausanne, Switzerland
e-mail: mauro.oddo@chuv.ch

P. Marques-Vidal
Department of Internal Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital, 1011 Lausanne, Switzerland

interventions to treat compromised $PbtO_2$ [10]. Whether increasing FiO_2 has beneficial or detrimental effect on the traumatized injured brain is still controversial [11–13].

Recently, clinical investigation found high levels of oxygen were associated with worse prognosis after severe TBI [14–16] and hypoxic-ischemic encephalopathy [17]. These observations suggest particular caution when using high FiO_2 levels and question the value of therapeutic supra-normal oxygen tension in patients with acute brain injury.

The exact mechanisms by which supra-normal oxygen tension may aggravate secondary cerebral damage have not been entirely elucidated in humans with acute brain injury. Experimental evidence suggests incremental levels of FiO_2 may exacerbate oxidative stress [18] and neuroinflammation [19]. Excess of exogenous extracellular glutamate seems one of the important mechanisms of hyperoxia-induced cerebral damage. Glutamate accounts for 80–90 % of the synapses in the brain and is the major excitatory neurotransmitter. The concentration of glutamate into the synaptic space rises dramatically after TBI, and failure of astrocytes to remove this excess of extracellular glutamate might ultimately lead to sustained excitotoxic damage and neuronal death, presumably mediated by excessive calcium influx via glutamate receptor operated ion channels [20]. Cultured astrocytes exposed to supra-normal FiO_2 showed a reduced capacity to protect oligodendrocyte progenitor cells against the toxic effects of exogenous glutamate, suggesting high FiO_2 alters glutamate homeostasis thereby leading to increased glutamate release and exacerbation of excitotoxic damage [21].

In humans with acute brain injury, the cerebral microdialysis (CMD) technique allows to measure dynamic changes of several cerebral extracellular markers upon therapeutic interventions, including glutamate [22, 23]. Elevated CMD glutamate is a marker of cerebral excitotoxicity and injury and is associated with worse outcome after severe TBI [24].

The objective of this study in patients with severe TBI monitored with CMD was to examine the relationship between incremental FiO_2 levels and cerebral extracellular glutamate. We hypothesized that high FiO_2 might exacerbate cerebral excitotoxicity in the acute ICU phase following TBI.

Materials and Methods

Patients

This was a retrospective analysis of a database of patients with severe TBI admitted to the Department of Intensive Care Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland. Ethical approval to conduct the study was obtained from local Ethical Committee, and waiver of consent was given due to the retrospective nature of this study.

Intracranial Monitoring

Indication for intracranial monitoring was severe TBI, defined by an admission or post-resuscitation Glasgow Coma Scale <9 and an abnormal CT-scan (Marshall score ≥ 2) [25]. Intracranial monitoring consisted of an intracranial pressure (ICP) sensor (Codman ICP MonitorinSystem, Raynham, MA, USA), a $PbtO_2$ probe (Licox® system, Integra Neurosciences, Plainsboro,NJ, USA) and a CMD catheter, as part of standard patient care at our institution. Cerebral extracellular glutamate was measured hourly using a CMA 70 microdialysis catheter with a 20 kDa cutoff (M Dialysis AB®, Stockholm, Sweden), perfused with artificial cerebrospinal fluid via a pump (M Dialysis AB; rate of 0.3 μL/min). Concentrations of CMD glutamate were measured immediately at the patient bedside with a kinetic enzymatic analyzer (ISCUS Flex®; M Dialysis AB). The three probes were inserted in the operating room by the neurosurgeon through a triple-lumen bolt (Integra® Neurosciences, Plainsboro, NJ, USA), and placed into subcortical white matter, usually into the right frontal lobe, in apparently normal brain. In all patients, a follow-up non-contrast head CT was performed at ≈ 24 h to confirm the correct placement of the intracranial monitoring.

General Management

All patients were treated according to a standard protocol for the treatment of severe TBI following a written institutional algorithm, according to international guidelines [26, 27] and as previously described [28]. Sedation/analgesia consisted of propofol and sufentanil. All patients were mechanically ventilated, aiming to maintain PaO_2 at 90–100 mmHg and $PaCO_2$ at 35–40 mmHg. Brain physiological targets were set to maintain ICP $<$ 20 mmHg, cerebral perfusion pressure (CPP = mean arterial pressure, measured via an intra arterial catheter—ICP) $>$ 60 mmHg, and $PbtO_2 >$ 20 mmHg. Blood glucose was targeted at 6–8 mmol/L using intravenous insulin. Ventilatory strategies in patients with TBI and acute respiratory distress syndrome (ARDS) were based on current algorithms for protective mechanical ventilation [29, 30].

Management of Elevated ICP and Compromised $PbtO_2$

Elevated ICP was defined as an ICP $>$ 20 mmHg for more than 5 min. First-line therapy of intracranial hypertension consisted of optimized sedation/analgesia, controlled normothermia (36–37 °C), and moderate hyperventilation ($PaCO_2$ 30–35 mmHg). If these interventions failed to

control ICP, osmotherapy with hypertonic saline (7.5 %, 100 mL, over 20 min) or mannitol (20 %, 0.5 g/kg, over 20 min) was given. Second-line therapies of elevated ICP consisted of mild hypothermia (34–35 °C), barbiturate coma (thiopental), or decompressive craniectomy in case of focal lesions.

Compromised $PbtO_2$ was defined as a $PbtO_2$ <20 mmHg, according to our threshold to start therapy. If compromised $PbtO_2$ was associated with elevated ICP, then therapy was first directed to control ICP. If ICP was normal, treatment of compromised $PbtO_2$ consisted of a multi-step interventional strategy, including increased FiO_2, MAP/CPP augmentation with vasopressors (norepinephrine), red blood cell transfusion (if hemoglobin was <9 g/dL), increasing PEEP (providing ICP remained <20 mmHg).

Data Collection and Analysis

Arterial blood gas analysis was performed at least every 2–3 h as part of routine care. Arterial blood measurements were matched to CMD samples collected the hour following the arterial blood sampling. For the purpose of this study, FiO_2 levels were categorized into four separate ranges, including (a) <40 %, (b) 41–60 %, (c) 61–80 %, and (d) >80 %. PaO_2 samples were categorized into three separate ranges, i.e., 60–99, 100–150, and >150 mmHg.

The relationship of the different ranges of FiO_2 and PaO_2 with CMD glutamate was explored using one-way analysis of variance (ANOVA) with Tukey's HSD post hoc test. Comparisons were adjusted for important brain and systemic covariates, including ICP, CPP, CMD lactate/pyruvate ratio, hemoglobin, $PaCO_2$, PaO_2, Marshall CT score, and APACHE II score. Correlation between $PbtO_2$ and CMD glutamate was analyzed with the Pearson's r linear correlation factor. Data analysis was performed using JMP-10® package software (SAS Institute, Cary, NC, USA). A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

From October 2009 to November 2013, a total of 1,130 CMD samples from 36 patients with severe TBI were analyzed. Patient baseline characteristics are summarized in Table 1. The majority of patients (31/36; 86 %) had diffuse lesions. Intracranial monitoring was placed in apparently normal brain in all patients. Median time from TBI to intracranial monitoring was 24 (interquartile range 24–120) hours. Median duration of monitoring was 4 (IQR 1–10) days. The median number of matched CMD/FiO_2 samples per patient was 33 (12–52). The majority of patients had no pulmonary dysfunction: 6/36 patients (17 %) were diagnosed with ARDS, according to the Berlin definitions [30]. Main cerebral and systemic variables are summarized in Table 2.

Table 1 Patient baseline characteristics

Variable	Value
Patient number	36
Age, years	40 ± 17
Female gender, number (%)	6 (17)
Median Glasgow Coma Scale (range)	6 (3–8)
Marshall CT score, number (%)	
1	2 (6)
2	23 (64)
3	6 (5)
4	2 (6)
5	2 (6)
6	1 (3)
APACHE II score	18 ± 5
Glasgow Outcome Score at 6 months, number (%)	
1 (death)	10 (27)
2 (vegetative state)	1 (3)
3 (severe disabilty)	7 (19)
4 (moderate disability)	9 (25)
5 (good recovery)	9 (25)

Data are presented as mean ± standard deviation, except otherwise stated

Table 2 Main cerebral and systemic physiologic variables

Variable	Value
Intracranial pressure (mmHg)	13 ± 8
Cerebral perfusion pressure (mmHg)	73 ± 9
Cerebral lactate/pyruvate ratio	30 ± 8
$PbtO_2$ (mmHg)	26 ± 8
FiO_2 (%)	50 ± 20
PaO_2 (mmHg)	121 ± 46
$PaCO_2$ (mmHg)	36 ± 4
Blood hemoglobin (g/dL)	11 ± 2
Systemic temperature (°C)	36 ± 1

Data are expressed as means (±standard deviation)

Incremental FiO_2 was Associated with Increased Cerebral Extracellular Glutamate

After adjusting for important cerebral ($PbtO_2$, intracranial pressure, cerebral perfusion pressure, CMD lactate/pyruvate ratio, Marshall CT score) and systemic ($PaCO_2$, PaO_2, hemoglobin, APACHE score) covariates, increased levels of FiO_2 were associated with a significant and progressive increase in CMD concentrations of glutamate (Fig. 1).

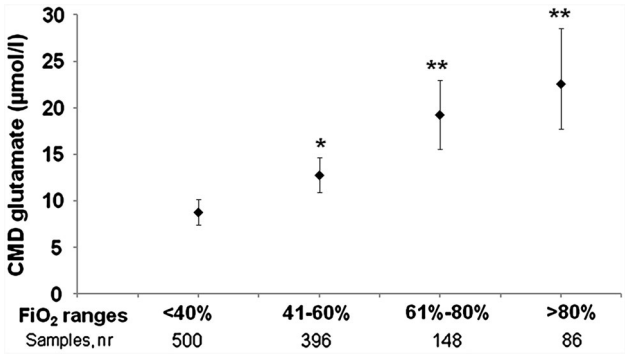

Fig. 1 Association between incremental fraction of inspired oxygen (FiO_2) and cerebral extracellular glutamate. The graph shows means (95 % confidence intervals) of cerebral microdialysis (CMD) glutamate according to ranges of FiO2. Total number of samples = 1130 from 36 patients; $*p < 0.05$ and $**p < 0.01$ for comparison with the reference range (FiO2 < 40%; ANOVA with Tukey's post hoc test).

Compared to the reference range [FiO_2 < 40 %: 8.8 (95 % confidence interval 7.4–10.2) µmol/L, higher FiO_2 levels were associated with increased CMD glutamate: 12.8 (10.9–14.7) µmol/L at FiO_2 41–60 % (adjusted $p = 0.02$ vs. FiO_2 < 40 %), 19.3 (15.6–23) µmol/L at FiO_2 61–80 % (adjusted $p < 0.0001$), and 22.6 (16.7–28.5) µmol/L at FiO_2 > 80 % (adjusted $p < 0.0001$). FiO_2-related increase of cerebral extracellular glutamate appeared clinically relevant (more than twofold increase from reference value) when FiO_2 was above 60 %. When separating samples in two subgroups, based on the time of monitoring (first 48 h; 311 samples vs. >48 h; 769 samples) we found comparable significant relationship between incremental FiO_2 and increased CMD glutamate (data not shown).

FiO_2-Related Increase of Cerebral Glutamate According to Baseline $PbtO_2$

We further analyzed whether the observed FiO_2-related increase of CMD glutamate varied according to baseline conditions of cerebral oxygenation. To examine that, we categorized CMD samples into two subgroups, according to simultaneous $PbtO_2$ value, defined as normal ($PbtO_2 \geq$ 20 mmHg) versus low ($PbtO_2$ < 20 mmHg). In brain hypoxic samples (Fig. 2a), FiO_2-related increase of CMD glutamate was significant starting at FiO_2 > 60 % [22.1 (13.6–30.6) µmol/L at FiO_2 > 80 % and 23.4 (14.6–32.2) at FiO_2 61–80 % vs. 6.0 (2.9–9.1) µmol/L at FiO_2 < 40 %, respectively, both adjusted $p < 0.05$], but it was not when FiO_2 was at 41–60 % [10.9 (6.9–14.9) vs. 6.0 (2.9–9.1) µmol/L, adjusted $p = 0.47$]. In samples with normal $PbtO_2 \geq$ 20 mmHg (Fig. 2b), we found CMD glutamate significantly increased already starting at FiO_2 > 40 %, similar to what observed in total samples.

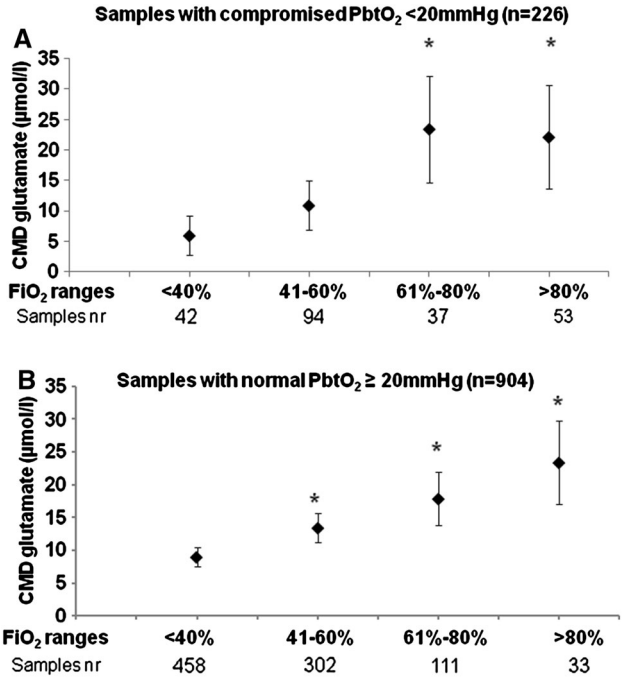

Fig. 2 Association between incremental fraction of inspired oxygen (FiO_2) and cerebral extracellular glutamate, according to baseline brain tissue oxygen tension ($PbtO_2$). The graph shows means (95 % confidence intervals) of cerebral microdialysis (CMD) glutamate according to ranges of FiO2 in the subgroup of samples with compromised PbtO2 <20 mmHg (panel A; n = 226 samples) and in samples with normal PbtO2 (panel B; n = 904 samples). $*p < 0.05$ and $**p < 0.01$ for comparison with the reference range (FiO2 < 40%; ANOVA with Tukey's post hoc test)

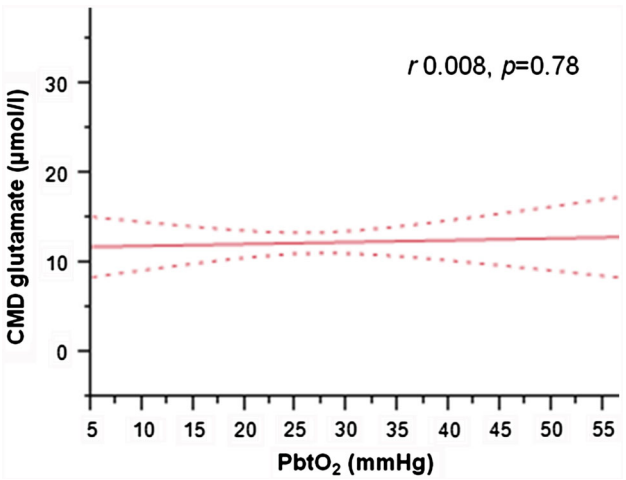

Fig. 3 Correlation between cerebral extracellular glutamate and brain tissue oxygen tension ($PbtO_2$). The graph shows Pearson's r linear correlation factor between cerebral microdialysis (CMD) glutamate and PbtO2, indicating no significant correlation between the two variables ($r = 0.008$, $p = 0.78$).

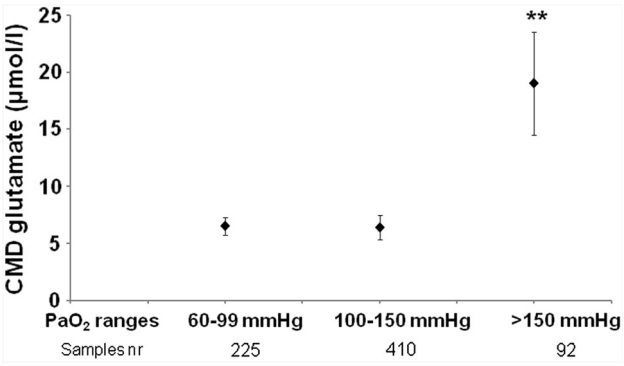

Fig. 4 Association between incremental partial pressure of arterial oxygen (PaO_2) and cerebral extracellular glutamate. The graph shows mean (95 % confidence intervals) of cerebral microdialysis (CMD) glutamate according to ascending ranges of PaO_2. $^{**}p < 0.01$ for comparison of PaO_2 >150 mmHg with PaO_2 60–99 mmHg and PaO_2 100–150 mmHg (ANOVA with Tukey's post hoc test)

Of note, we found no significant correlation between $PbtO_2$ and CMD glutamate (Pearson's r 0.008, $p = 0.78$, Fig. 3), thereby indicating no direct relationship between the extent of post-TBI brain hypoxia and the level of cerebral glutamate. Therefore, increased CMD glutamate observed in the setting of high FiO_2 was plausibly not due to a greater extent of brain injury.

Relationship Between PaO_2 and Cerebral Extracellular Glutamate

The relationship between hyperoxia (defined as a PaO_2 >150 mmHg) and CMD glutamate was assessed by categorizing PaO_2 samples into three separate ranges, i.e., 60–99, 100–150, and >150 mmHg. A total of 727 matched CMD-PaO_2 samples were available for this analysis (Fig. 4): samples with PaO_2 >150 mmHg were associated with significantly higher levels of CMD glutamate [19 (14.6–23.5) vs. 6.4 (5.3–7.1) µmol/L at PaO_2 100–150 mmHg and 6.5 (5.7–7.2) µmol/L at PaO_2 of 60–99 mmHg, respectively, adjusted $p < 0.001$ for comparison with both PaO_2 ranges].

Discussion

The findings of this retrospective cohort study of patients with severe TBI can be summarized as follows: (1) incremental FiO_2 levels >40 % were associated with a progressive marked elevation (up to threefold for samples with FiO_2 >60 %) of cerebral extracellular glutamate, independently from baseline main cerebral ($PbtO_2$, intracranial pressure, cerebral perfusion pressure, CMD lactate/pyruvate ratio, Marshall score) and systemic ($PaCO_2$, PaO_2, hemoglobin, APACHE score) covariates; (2) the threshold for FiO_2-related increase in CMD glutamate varied according to baseline $PbtO_2$, being significant when FiO_2 was above 40 % for samples with normal $PbtO_2$, while among brain hypoxic samples CMD glutamate started to raise significantly only when FiO_2 was above 60 %; (3) no correlation between CMD glutamate and $PbtO_2$ was found, therefore the observed relationship between high FiO_2 and increased cerebral glutamate may not be due to a greater post-traumatic injury severity; and (4) hyperoxia (defined by a PaO_2 >150 mmHg) was similarly associated with an average threefold increase of cerebral extracellular glutamate.

Oxygen Therapy After TBI

Whether hyperoxia is beneficial or detrimental following acute severe brain injury remains controversial [11–13]. Based on the evidence that brain hypoxia is an important determinant of secondary cerebral damage and outcome after severe TBI [1], oxygen supply with normobaric FiO_2 is routinely provided in this setting, often to correct compromised $PbtO_2$. Beneficial effects of normobaric hyperoxia, e.g., a reduction of the volume of post-traumatic contusion, have been reported in animal models of severe TBI [31–34]. However, in other experimental settings such as in pig models of TBI, supra-normal FiO_2 did not attenuate post-traumatic elevation of cerebral extracellular lactate/pyruvate ratio, despite improving brain oxygenation [35]. Clinical investigation also provided controversial results. Nortje et al. [36], in a cohort of 11 TBI patients monitored with CMD, found that increasing FiO_2 from 35 to 50 % was associated only with a slight (and possibly clinically irrelevant) decrease of cerebral extracellular lactate/pyruvate ratio. Using brain positron emission tomography, Diringer et al. [37] found that 100 % FiO_2 did not improve brain oxygen metabolism in patients with severe TBI, in line with previous clinical studies that found no changes of brain lactate/pyruvate ratio and no effects on cerebral glucose metabolism following short trials of normobaric 100 % FiO_2 [38]. The value of therapeutic supranormal oxygen has been recently questioned by observational cohort studies reporting an association between hyperoxia and higher in-hospital mortality in subjects with acute brain injury following severe TBI [15, 16] and cardiac arrest [39–41].

Possible Mechanisms of FiO_2-Induced Brain Toxicity: The Role of Excessive Glutamate Release

Several mechanisms by which increased FiO_2 may be harmful following acute brain injury have been proposed. Among these, increased oxidative stress has been frequently reported and is probably a leading factor involved

in FiO_2 toxicity [18]. Other potential mechanisms include cerebral vasoconstriction [42] and exacerbation of neuroinflammation [19]. Glutamate accounts for 80–90 % of the synapses in the brain and is the major excitatory neurotransmitter. Maintenance of glutamate homeostasis is essential for the injured brain: following TBI, concentration of glutamate into the synaptic space may rise dramatically, and failure of brain cells (mainly astrocytes) to remove this excess of extracellular glutamate might lead to excitotoxic damage and eventually cell death [20]. The role of glutamate in contributing to the toxicity of supra-normal FiO_2 has been shown in models of acute brain [21] and lung [43] injury. Our clinical study using the CMD technique to measure cerebral extracellular concentrations of glutamate appears to confirm previous experimental findings. Our results also suggest that impairment of glutamate homeostasis in the injured brain with subsequent increased cerebral excitotoxic damage may be one of the mechanisms by which high FiO_2 exacerbates brain injury. By leading to increased glutamate release and excitability, one potential mechanism of oxygen-induced toxicity is by exacerbating infra-clinical seizures. Indeed, central nervous system oxygen toxicity seizures are well described [44]. A relationship between increased CMD glutamate and seizures has also been described [45, 46]. We did not systematically monitor EEG continuously in these patients therefore we do not have data to support this hypothesis. Further clinical investigation is warranted.

Clinical Implications

An important reason for using high FiO_2 is low $PbtO_2$; indeed, incremental FiO_2 is frequently used to correct brain hypoxia [9]. When adjusting for important cerebral (including $PbtO_2$, but also ICP, CPP, CMD lactate/pyruvate ratio, and the Marshall CT score) and systemic variables, we found that FiO_2-related increase of CMD glutamate was independent of baseline $PbtO_2$ and of the severity of injury. Elevated CMD glutamate is a marker of brain injury [24]: the fact that CMD glutamate was not correlated to patient baseline $PbtO_2$ (Fig. 3) seems to reinforce the notion that, in our study, increased cerebral glutamate upon high FiO_2 was not just because of increased severity of brain injury. Although FiO_2-related increase of CMD glutamate was independent from $PbtO_2$ (i.e., it occurred irrespective of baseline brain oxygen), we found the threshold for increased cerebral glutamate varied according to initial $PbtO_2$ levels, i.e., it was lower for samples with normal $PbtO_2$ ($FiO_2 > 40$ %) than for those with compromised $PbtO_2$ ($FiO_2 > 60$ %).

Strict control of systemic oxygenation with avoidance of high FiO_2 may be recommended in patients with severe TBI. Our findings that hyperoxia ($PaO_2 > 150$ mmHg) was also associated with a significant and clinically relevant increase (about threefold, see Fig. 4) of cerebral extracellular glutamate seem to support this concept. Finally, elevation of CMD glutamate >10 μmol/L is also a marker of worse neurological outcome after severe brain injury [24]. Therefore, the association of high $FiO_2 > 60$ % with elevated CMD glutamate ≈ 15–20 μmol/L suggests that supra-normal oxygen levels might potentially aggravate patient prognosis. Altogether, our findings appear more in favor of controlled (aiming at normal FiO_2 and PaO_2 ranges) rather than aggressive (aiming to supra-normal FiO_2 and PaO_2 ranges) normobaric oxygen therapy in the setting of severe TBI.

Study Limitations

The main limitation of this study is that it is a retrospective observational analysis. However, patients were all treated with a written standardized algorithm for the management of severe TBI and data were from a homogenous cohort of subjects with predominantly diffuse injury, in whom intracranial monitoring (including CMD and $PbtO_2$) was located in apparently normal brain. These data are to be considered as preliminary and further investigation is needed to examine the cerebral effects of high FiO_2 in patients with severe TBI and other acute cerebral conditions. Second, given the nature of the study, we were only able to estimate the intensity (i.e., the percentage of administered FiO_2) of normobaric oxygen therapy, but we did not assess its duration, i.e., the differential cerebral effects of transient versus prolonged supra-normal FiO_2. For the same reason, time period between FiO_2 adjustments and changes in CMD glutamate within each patient could not be examined. In clinical prospective studies describing favorable cerebral effects of supplemental normobaric oxygen, short (generally up to 2 h) FiO_2 trials were administered [47, 48]. One study in severe TBI patients reported beneficial effects of prolonged exposure to 100 % FiO_2 on cerebral energy metabolism [49]. Our study did not allow us to investigate the effect of short versus prolonged oxygen therapy and additional studies are needed. We examined a large number of samples (1,130) from a relatively large sample-size monitored early (median 24 h) after TBI, in whom monitoring lasted for a median of 4 days. Our associations are therefore representative of the acute ICU phase of TBI, following initial resuscitation and insertion of intracranial monitoring, as previous prospective interventional studies. Still, it is important to underline that we did not study the very early phase of TBI; therefore, we cannot examine whether supplemental high FiO_2 administered immediately after TBI may be neuroprotective, as shown by some experimental studies [31]. Also, we did

categorize FiO_2 into four separate representative quartiles, but we did not calculate the true "hyperoxia burden" using area under the curve analysis, which would have strengthened the analysis. Our findings are applicable to patients with TBI without underlying acute lung injury, which represented the majority of our cohort (more than 80 %); therefore, additional data are needed to explore the cerebral effects of supplemental oxygen in patients with TBI and lung dysfunction or polytrauma. Finally, we reported an association between normobaric oxygen therapy and increased cerebral excitotoxicity, however, we did not assess the potential beneficial effect of hyperbaric oxygen therapy, as described by Rockswold et al. [50, 51] in patients with severe TBI.

Conclusions

The results of this CMD study suggest that incremental FiO_2 levels are associated with an increase in cerebral extracellular glutamate in patients with severe TBI, independent of main cerebral and systemic physiologic ($PbtO_2$, ICP, CPP, brain lactate/pyruvate ratio, PaO_2, $PaCO_2$, blood hemoglobin) and clinical (Marshall CT score, APACHE II score) variables. Elevation of cerebral glutamate was particularly relevant (threefold increase, up to $\approx$15–20 μmol/L) when FiO_2 was above 60 % and in hyperoxic conditions (PaO_2 above 150 mmHg). These preliminary data suggest supplemental high FiO_2 may be harmful and favor controlled (aiming at normal FiO_2 and PaO_2 ranges) rather than aggressive (aiming to supra-normal FiO_2 and PaO_2) normobaric oxygen therapy in the setting of severe TBI.

Acknowledgments This work was supported by grants from the Swiss National Science Foundation (Grant No. 320030_138191, to Mauro Oddo), the Novartis Foundation for Biomedical Research (to Mauro Oddo) and the Société Française d'Anesthésie et Réanimation (SFAR) (to Hervé Quintard). The authors thank Professor Lucas Liaudet, MD, for helpful scientific discussion.

Conflict of interest All authors declare they have no conflicts of interest to report.

References

1. Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69:1037–45 discussion 45.
2. McCarthy MC, Moncrief H, Sands JM, et al. Neurologic outcomes with cerebral oxygen monitoring in traumatic brain injury. Surgery. 2009;146:585–90; discussion 90-1.
3. Narotam PK, Morrison JF, Nathoo N. Brain tissue oxygen monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg. 2009;111:672–82.
4. Spiotta AM, Stiefel MF, Gracias VH, et al. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. J Neurosurg. 2010;113:571–80.
5. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg. 2005;103:805–11.
6. Fletcher JJ, Bergman K, Blostein PA, Kramer AH. Fluid balance, complications, and brain tissue oxygen tension monitoring following severe traumatic brain injury. Neurocrit Care. 2010;13:47–56.
7. Martini RP, Deem S, Yanez ND, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. J Neurosurg. 2009;111:644–9.
8. Meixensberger J, Jaeger M, Vath A, Dings J, Kunze E, Roosen K. Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. J Neurol Neurosurg Psychiatry. 2003;74:760–4.
9. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. Neurocrit Care. 2011;14:361–9.
10. Kumaria A, Tolias CM. Normobaric hyperoxia therapy for traumatic brain injury and stroke: a review. Br J Neurosurg. 2009;23:576–84.
11. Diringer MN. Hyperoxia: good or bad for the injured brain? Curr Opin Crit Care. 2008;14:167–71.
12. Beynon C, Kiening KL, Orakcioglu B, Unterberg AW, Sakowitz OW. Brain tissue oxygen monitoring and hyperoxic treatment in patients with traumatic brain injury. J Neurotrauma. 2012;29:2109–23.
13. Sjoberg F, Singer M. The medical use of oxygen: a time for critical reappraisal. J Intern Med. 2013;274:505–28.
14. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg. 2012;147:1042–6.
15. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry 2014;85(7):799–805.
16. Davis DP, Meade W, Sise MJ, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009;26:2217–23.
17. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation. 2011;123:2717–22.
18. Solberg R, Longini M, Proietti F, Vezzosi P, Saugstad OD, Buonocore G. Resuscitation with supplementary oxygen induces oxidative injury in the cerebral cortex. Free Radic Biol Med. 2012;53:1061–7.
19. Blasiole B, Bayr H, Vagni VA, et al. Effect of hyperoxia on resuscitation of experimental combined traumatic brain injury and hemorrhagic shock in mice. Anesthesiology. 2013;118:649–63.
20. McKenna MC. The glutamate–glutamine cycle is not stoichiometric: fates of glutamate in brain. J Neurosci Res. 2007;85:3347–58.
21. Schmitz T, Ritter J, Mueller S, Felderhoff-Mueser U, Chew LJ, Gallo V. Cellular changes underlying hyperoxia-induced delay of white matter development. J Neurosci. 2011;31:4327–44.
22. Hillered L, Vespa PM, Hovda DA. Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma. 2005;22:3–41.
23. Oddo M, Villa F, Citerio G. Brain multimodality monitoring: an update. Curr Opin Crit Care. 2012;18:111–8.
24. Timofeev I, Carpenter KL, Nortje J, et al. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. Brain. 2011;134:484–94.

25. Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma. 1992;9(Suppl 1):S287–92.
26. Bratton SL, Chestnut RM, Ghajar J, McConnell HF, Harris OA, Hartl R, Manley GT, et al. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. J Neurotrauma. 2007;24(Suppl 1):S65–70.
27. Narayan RK, Kishore PR, Becker DP, Ward JD, Enas GG, Greenberg RP, Domingues Da Silva A, et al. Guidelines for the management of severe traumatic brain injury. VII. Intracranial pressure monitoring technology. J Neurotrauma. 2007;24(Suppl 1): S45–54.
28. Sala N, Suys T, Zerlauth JB, et al. Cerebral extracellular lactate increase is predominantly nonischemic in patients with severe traumatic brain injury. Journal Cereb Blood Flow Metab. 2013;33:1815–22.
29. Brower RG, Rubenfeld GD. Lung-protective ventilation strategies in acute lung injury. Crit Care Med. 2003;31:S312–6.
30. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA J Am Med Assoc. 2012;307:2526–33.
31. Muthuraju S, Pati S, Rafiqul M, Abdullah JM, Jaafar H. Effect of normabaric hyperoxia treatment on neuronal damage following fluid percussion injury in the striatum of mice: a morphological approach. J Biosci. 2013;38:93–103.
32. Palzur E, Vlodavsky E, Mulla H, Arieli R, Feinsod M, Soustiel JF. Hyperbaric oxygen therapy for reduction of secondary brain damage in head injury: an animal model of brain contusion. J Neurotrauma. 2004;21:41–8.
33. Moody RA, Mead CO, Ruamsuke S, Mullan S. Therapeutic value of oxygen at normal and hyperbaric pressure in experimental head injury. J Neurosurg. 1970;32:51–4.
34. Chen T, Qian YZ, Di X, Rice A, Zhu JP, Bullock R. Lactate/glucose dynamics after rat fluid percussion brain injury. J Neurotrauma. 2000;17:135–42.
35. Rostami E, Rocksen D, Ekberg NR, Goiny M, Ungerstedt U. Brain metabolism and oxygenation in healthy pigs receiving hypoventilation and hyperoxia. Respir Physiol Neurobiol. 2013;189:537–42.
36. Nortje J, Coles JP, Timofeev I, et al. Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: preliminary findings. Crit Care Med. 2008;36:273–81.
37. Diringer MN, Aiyagari V, Zazulia AR, Videen TO, Powers WJ. Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury. J Neurosurg. 2007;106:526–9.
38. Magnoni S, Ghisoni L, Locatelli M, et al. Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: a microdialysis study. J Neurosurg. 2003;98:952–8.
39. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA J Am Med Assoc. 2010;303: 2165–71.
40. Rincon F, Kang J, Maltenfort M, et al. Association between hyperoxia and mortality after stroke: a multicenter cohort study. Crit Care Med. 2014;42:387–96.
41. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12:R156.
42. Rangel-Castilla L, Lara LR, Gopinath S, Swank PR, Valadka A, Robertson C. Cerebral hemodynamic effects of acute hyperoxia and hyperventilation after severe traumatic brain injury. J Neurotrauma. 2010;27:1853–63.
43. Wang M, Luo Z, Liu S, et al. Glutamate mediates hyperoxia-induced newborn rat lung injury through *N*-methyl-D-aspartate receptors. Am J Respir Cell Mol Biol. 2009;40:260–7.
44. D'Agostino DP, Pilla R, Held HE, et al. Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. Am J Physiol Regul Integr Comp Physiol. 2013; 304:R829–36.
45. Vespa P, Prins M, Ronne-Engstrom E, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. J Neurosurg. 1998;89:971–82.
46. Thomas PM, Phillips JP, Delanty N, O'Connor WT. Elevated extracellular levels of glutamate, aspartate and gamma-aminobutyric acid within the intraoperative, spontaneously epileptiform human hippocampus. Epilepsy Res. 2003;54:73–9.
47. Puccio AM, Hoffman LA, Bayir H, et al. Effect of short periods of normobaric hyperoxia on local brain tissue oxygenation and cerebrospinal fluid oxidative stress markers in severe traumatic brain injury. J Neurotrauma. 2009;26:1241–9.
48. Tisdall MM, Tachtsidis I, Leung TS, Elwell CE, Smith M. Increase in cerebral aerobic metabolism by normobaric hyperoxia after traumatic brain injury. J Neurosurg. 2008;109:424–32.
49. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. J Neurosurg. 2004;101:435–44.
50. Rockswold SB, Rockswold GL, Zaun DA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg. 2010;112:1080–94.
51. Rockswold SB, Rockswold GL, Zaun DA, Liu J. A prospective, randomized phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. J Neurosurg. 2013;118: 1317–28.