Intensive Care Med (2022) 48:1772–1774
https://doi.org/10.1007/s00134-022-06903-x

EDITORIAL

High oxygen level in traumatic brain injury patients. Never ending story?

Karim Asehnoune[1,4,5*], Fabio S. Taccone[2] and Mervyn Singer[3]

Oxygen is crucial for aerobic cellular metabolism; however, mitochondrial respiration can also form reactive oxygen species (ROS) [1], the level of which directly correlates with oxygen exposure [2]. It is, therefore, obvious that increasing oxygen administration (i.e., inspiratory oxygen fraction, FiO_2) will increase the inspired O_2 concentration and, consequently, the level of ROS production. Antioxidant defenses generally protect the cell and allow ROS, at low concentrations, to participate physiologically in several signaling pathways. However, when ROS concentrations become excessive and defenses are overwhelmed, harmful effects are observed on cell organelles. A major consequence of rapid, excessive ROS production is the initiation of an inflammatory response that may result in organ failure [3]. These pathophysiological effects of ROS highlight the possible dangers of hyperoxia and indicate that supraphysiological levels of arterial partial pressure of oxygen (PaO_2) are not without risk. The situation is rather complex in the clinical setting as hypoxemia is also associated with an increased risk of death in critically ill patients [4]. Thus, a risk–benefit balance needs to be struck between treating injurious levels of hypoxemia yet avoiding supranormal oxygen exposure in this setting, acknowledging that not all patients might be harmed equally by hyperoxia.

Cerebral ischemia is a major cause of secondary brain injury after traumatic brain injury (TBI). Improving cerebral oxygen delivery is therefore a major goal and is generally obtained by increasing cerebral perfusion pressure and treating brain swelling. Hyperoxia is also considered a therapeutic option to minimize tissue hypoxia in this setting. Studies indicate that hyperoxia increases regional brain oxygen tension (i.e., brain tissue oxygen monitoring, $PbtO_2$) [5]; this may theoretically enhance mitochondrial function that is disturbed following brain injury [6] and, therefore, oxygen metabolism. Hyperoxia may also facilitate oxygen diffusion into brain cells, even in cases of interstitial edema or microvascular impairment. Nevertheless, the effects on oxygen delivery are minimal; as such, the role of hyperoxia in TBI patient remains debatable [7].

In situations of several cellular impairment (e.g., tissue contusion or cellular swelling) with resulting mitochondrial damage, hyperoxia may be both ineffective and increase local inflammation [6]. Hyperoxia increases cerebral vasoconstriction and could potentially reduce tissue perfusion [8]. Prolonged hyperoxia may also be deleterious to other organs, in particular the lungs, and can increase peripheral vascular resistance [9], thereby increasing the risk of extra-cerebral complications.

To our knowledge, only one trial has specifically addressed the impact of normobaric hyperoxia on mechanically ventilated patients with septic shock [10]. This trial was stopped prematurely because of a signal to harm in the hyperoxia group (28 day mortality 43% vs 35%; $p=0.12$). A post hoc analysis found the mortality difference (57.4% vs. 44.3%, $p=0.054$) was solely in those fulfilling the Sepsis-3 criteria for septic shock of vasopressor requirement and persisting hyperlactatemia > 2 mmol/l [11]. Multivariate analysis revealed an independent association between hyperoxia and mortality both at days 28 and 90. In patients with normal lactate levels, there was no impact of hyperoxia on mortality nor other outcomes.

A meta-analysis in acute brain-injured patients found that hyperoxia was associated with an increased risk

*Correspondence: karim.asehnoune@chu-nantes.fr
[4] Head, Anaesthesia and Surgical Critical Care Department, University Hospital of Nantes, Hôtel Dieu, 44000 Nantes, France
Full author information is available at the end of the article

of poor neurological outcome [12]. Considering the uncertainty regarding the level of oxygen that should be applied to TBI patients, the study of Rezoagli et al. published in this issue of Intensive Care Medicine [13] has added some relevant insights. This trial was a sub-study of two multicenter, prospective, observational, cohort studies totaling 1243 TBI patients performed in Europe and Australia. High values of arterial blood oxygen were independently associated with 6-month mortality in the CENTER-TBI cohort; another important result was that the severity of brain injury did not influence the relationship between hyperoxia and mortality; more than 50% of patients were exposed to hyperoxia, defined as PaO_2 levels > 120 mmHg, indicating that this event is quite frequent in TBI patients across centers. The authors also report that the average daily swing of FiO_2 correlated with the mortality rate.

These findings are clinically significant. The variability in oxygen management could be explained by the absence of consensus in the current literature to define hyperoxia. The PaO_2 threshold used in this study is in line with the latest guidelines from the European Society of Intensive Care Medicine (ESICM) which proposed, with a low level of evidence, to avoid values > 120 mmHg [14]. Setting this limit may be useful for the attending intensive care unit (ICU) physician to avoid potential harm to TBI patients. Titrating oxygen delivery by tissue monitoring (i.e., brain oxygen partial pressure or saturation) could be considered, but more data are needed to validate this approach.

Some limitations deserve comment. The population of TBI patients in this study was highly heterogenous. In particular, a sub-group of patients had brain tissue oxygen monitoring; it was recently suggested that elevating PaO_2 above 120 mmHg in patients with low $PbtO_2$ could be a valuable approach [14]. The results were not fully validated in the external OzENTER cohort, probably because the sample size was too small ($n = 149$). Second, the authors provided PaO_2 values only over the first week of ICU stay and the number of available PaO_2 measurements was relatively low. This precludes a more advanced analysis of oxygen exposure and the assessment of potential late oxygen toxicity in this population. Third, there was no information on withdrawal of care practices nor in-hospital complications, that would be unrelated to oxygen exposure but still relevant to overall mortality. Finally, only a few patients had very high mean PaO_2 values (i.e. > 200 mmHg); as outliers, this may have biased the association between PaO_2 and outcome.

Oxygen should be considered as a drug that is used almost ubiquitously in ICU patients but should be carefully titrated to a prescribed target. In particular, hyperoxia may cause harm. Currently, there is no evidence to support the use of hyperoxia in ICU patients with severe TBI. Avoiding high FiO_2, other than for controlling hypoxemia, should be considered in all patients.

Author details
[1] Department of Anaesthesia and Critical Care, CHU Nantes, Nantes Université, Hôtel Dieu, 44000 Nantes, France. [2] Department of Intensive Care, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium. [3] Mervyn Singer, Bloomsbury Institute of Intensive Care, University College London, London, UK. [4] Head, Anaesthesia and Surgical Critical Care Department, University Hospital of Nantes, Hôtel Dieu, 44000 Nantes, France. [5] Lab Inserm, UMR 1064 CR2TI | Team 6, Nantes, France.

Received: 21 September 2022 Accepted: 28 September 2022
Published: 20 October 2022

References

1. Asfar P, Singer M, Radermacher P (2015) Understanding the benefits and harms of oxygen therapy. Intensive Care Med 41(6):1118–1121. https://doi.org/10.1007/s00134-015-3670-z
2. Turrens J (2003) Mitochondrial formation of reactive oxygen species. J Physiol 552(Pt 2):335–344. https://doi.org/10.1113/jphysiol.2003.049478
3. Singer M, Young PJ, Laffey JG, Asfar P, Taccone FS, Skrifvars MB, Meyhoff CS, Radermacher P (2021) Dangers of hyperoxia. Crit Care 25(1):440. https://doi.org/10.1186/s13054-021-03815-y
4. Lee BK, Jeung KW, Lee HY, Lee SJ, Jung YH, Lee WK et al (2014) Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. Am J Emerg Med 32:55–60
5. Longhi L, Valeriani V, Rossi S, De Marchi M, Egidi M, Stocchetti N (2002) Effects of hyperoxia on brain tissue oxygen tension in cerebral focal lesions. Acta Neurochir Suppl 81:315–317. https://doi.org/10.1007/978-3-7091-6738-0_80
6. Verweij BH, Muizelaar JP, Vinas FC, Peterson PL, Xiong Y, Lee CP (2000) Impaired cerebral mitochondrial function after traumatic brain injury in humans. J Neurosurg 93(5):815–820. https://doi.org/10.3171/jns.2000.93.5.0815
7. Diringer MN (2008) Hyperoxia-good or bad for the injured brain? Curr Opin Crit Care 14(2):167–171. https://doi.org/10.1097/MCC.0b013e3282f57552
8. Bulte DP, Chiarelli PA, Wise RG, Jezzard P (2007) Cerebral perfusion response to hyperoxia. J Cereb Blood Flow Metab 27(1):69–75. https://doi.org/10.1038/sj.jcbfm.9600319
9. Mak S, Egri Z, Tanna G, Colman R, Newton GE (2002) Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. Am J Physiol Heart Circ Physiol 282(6):H2414–H2421. https://doi.org/10.1152/ajpheart.00947.2001
10. Asfar P, Schortgen F, Boisramé-Helms J, Charpentier J, Guérot E, Megarbane B et al (2017) HYPER2S Investigators; REVA research network. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med 5:180–190
11. Demiselle J, Wepler M, Hartmann C, Radermacher P, Schortgen F, Meziani F, Singer M, Seegers V, Asfar P, HYPER2S investigators (2018) Hyperoxia toxicity in septic shock patients according to the Sepsis-3 criteria: a post hoc analysis of the HYPER2S trial. Ann Intensive Care 8:90
12. Hirunpattarasilp C, Shiina H, Na-Ek N, Attwell D (2022) The effect of hyperoxemia on neurological outcomes of adult patients: a systematic review and meta-analysis. Neurocrit Care. https://doi.org/10.1007/s12028-021-01423-w
13. Rezoagli E, Petrosino M, Rebora P, Menon DK, Mondello S, Cooper DJ, Maas AIR, Wiegers EJA, Galimberti S, Citerio G, on behalf of the CENTER-TBI and OzENTER-TBI Participants and Investigators. High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury. Insights from CENTER-TBI and OzENTER-TBI. Intensive Care Med. https://doi.org/10.1007/s00134-022-06884-x

14. Chesnut R, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, Arrastia RD, Diringer M, Figaji A, Gao G, Geocadin R, Ghajar J, Harris O, Hoffer A, Hutchinson P, Joseph M, Kitagawa R, Manley G, Mayer S, Menon DK, Meyfroidt G, Michael DB, Oddo M, Okonkwo D, Patel M, Robertson C, Rosenfeld JV, Rubiano AM, Sahuquillo J, Servadei F, Shutter L, Stein D, Stocchetti N, Taccone FS, Timmons S, Tsai E, Ullman JS, Vespa P, Videtta W, Wright DW, Zammit C, Hawryluk GWJ (2020) A management algorithm for adult patients with both brain oxygen and intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 46(5):919–929. https://doi.org/10.1007/s00134-019-05900-x