The Journal of Emergency Medicine, Vol. 65, No. 6, pp. e495–e510, 2023
© 2023 Elsevier Inc. All rights reserved.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2023.08.002

Clinical Review

The Effect of Early Severe Hyperoxia in Adults Intubated in the Prehosptial Setting or Emergency Department: A Scoping Review

George Yusin, MD,* Charlotte Farley, MD,* Charles Scott Dorris, MLIS,† Sofiya Yusina, AB,‡ Saad Zaatari, MD,*,§ and Munish Goyal, MD*,§

*Georgetown University School of Medicine, Washington, District of Columbia, †Georgetown University Medical Center, Washington, District of Columbia, ‡New York University Grossman School of Medicine, New York, NY, and §Department of Emergency Medicine, MedStar Health, Washington, District of Columbia

Reprint Address: George Yusin, MD, 12381 Kelly Sands Way, Fort Myers, FL 33908

□ **Abstract—Background: The detrimental effects of hyperoxia exposure have been well-described in patients admitted to intensive care units. However, data evaluating the effects of short-term, early hyperoxia exposure in patients intubated in the prehospital setting or emergency department (ED) have not been systematically reviewed. Objective: Our aim was to quantify and describe the existing literature examining the clinical outcomes in ED patients exposed to hyperoxia within the first 24 h of mechanical ventilation. Methods: This review was performed in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping reviews. Two rounds of review using Rayyan QCRI software were performed for title and abstract screening and full-text search. Of the 2739 articles, 27 articles were retrieved after initial screening, of which 5 articles were excluded during the full-text screening, leaving 22 articles for final review and data extraction. Results: Of 22 selected publications, 9 described patients with traumatic brain injury, 6 with cardiac arrest, 3 with multisystem trauma, 1 with stroke, 2 with septic shock, and 1 was heterogeneous. Three studies were randomized controlled trials. The available data have widely heterogeneous definitions of hyperoxia exposure, outcomes, and included populations, limiting conclusions. Conclusions: There is a paucity of data that examined the effects of severe hyperoxia exposure in the acute, post-intubation phase of the prehospital and ED settings. Further research with standardized definitions is needed to provide more detailed guidance regarding early oxygen titration in intubated patients.** **© 2023 Elsevier Inc. All rights reserved.**

□ **Keywords—hyperoxia; early hyperoxia; emergency department; mechanical ventilation; intubation; traumatic brain injury; cardiac arrest; trauma**

Introduction

The volume of critical care delivered in emergency departments (EDs) has been increasing over the last decade (1). Approximately 250,000 patients are mechanically ventilated in EDs annually in the United States (1). Mechanically ventilated patients are staying longer in the ED prior to intensive care unit (ICU) transfer (2). Prolonged boarding is associated with numerous adverse outcomes, including increased mortality (2). To avoid hypoxemia, clinicians administer excessive and unregulated doses of oxygen for extended durations, even when pulse oximetry indicates adequate oxygenation (3). In a study of mechanically ventilated ICU patients with acute lung injury, 74% were exposed to excessive fraction of inspired oxygen (FiO_2) for 17 h post intubation, on average.

The deleterious effects of excess oxygen are well-described. In animal models, hyperoxia exposure is associated with lung injury, inflammation, impaired hemo-

Received: 6 April 2023; Final submission received: 16 July 2023;
Accepted: 10 August 2023

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

dynamics, and reduced oxygen consumption (4–6). In humans, a systematic review and meta-analysis found that liberal oxygen therapy was associated with increased mortality in a dose-dependent fashion (7). Although these findings have important implications, the authors did not describe when enrollment began during the patients' care. Many studies of critically ill patients randomize after ICU arrival, not accounting for initial hours of potential exposure to hyperoxia.

Exposure to extreme hyperoxia in the early phases of resuscitation may have substantial clinical effects. The unique aim of this review was to quantify and describe the literature that examined clinical outcomes in ED patients exposed to hyperoxia in the first 24 h post intubation.

Materials and Methods

We conducted this review in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (Figure 1) (8).

Eligibility

We analyzed studies that included patients with exposure to hyperoxia within an ED or prehospital setting. Studies were excluded if they included patients not intubated within the first 24 h of care; included patients with acute respiratory distress syndrome prior to intubation; did not describe oxygen exposure measurement (e.g., partial pressure of oxygen [PaO_2] or saturation of peripheral oxygen [SpO_2]); were neonatal, pediatric, or animal populations; or were conference abstracts, review articles, or clinical practice guidelines.

Information Sources

We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (all via Ovid), Web of Science Core Collection, and Cumulative Index to Nursing and Allied Health Literature via EBSCOhost from the database inception to the search date (June 1, 2021).

Search Strategy

The systematic searches comprised a combination of keywords and database-specific subject headings for the concepts of hyperoxia and intubation. See the Appendix for full, reproducible search strategies. We removed duplicates using EndNote X9 (Clarivate Analytics) and uploaded the resulting citations to Rayyan for screening (9).

Selection Process

Title/abstract eligibility screening was conducted independently by four blinded authors. For a study to be included, most of the patients in an original research publication had to originate in the ED or prehospital, and the exposure to hyperoxia and measured exposure should have occurred within 24 h of encounter. On completion of the screening process, we resolved any conflicts as a team. Full-text screening was completed by at least two authors. After this phase, the included articles were categorized based on the disease process, and the data from each publication were recorded (Tables 1–3).

Data Extraction/Collection

Two authors independently extracted the following variables from the studies: First author, year, sample size, study design, inclusion criteria, definition of hyperoxia exposure, definition of the reference group, and primary outcome in the exposed group. Any discrepancies were resolved as a team.

Results

Most studies involved patients who experienced a traumatic brain injury (TBI) and cardiac arrest. Therefore, we focused on these in our results. Information on other patient populations is available in the Supplementary Material.

TBI

Nine studies were identified that focused on patients with TBI (10,16,18–24). Common inclusion criteria were Glasgow Coma Scale (GCS) score < 8, intubated, or Abbreviated Injury Scale score ≥ 3. Most studies excluded patients lacking arterial blood gas (ABG) data, deceased < 12 h after admission, or transferred to another facility. Study participants had initial encounters in the ED, a level I trauma center, or in an ICU. Most studies did not provide mechanism of injury, although some stratified the TBIs based on severity or differentiated between blunt and penetrating trauma. Significant variability was observed in the mean age of the patients, as shown in Table 1. Except for the study by Alali et al., in which 93% of participants were female, all studies had predominantly male populations (10).

The definitions of hyperoxia and normoxia varied widely among studies. The threshold for defining hyperoxia varied from a $PaO_2 > 100$ mm Hg to > 300 mm Hg. Normoxia was typically defined as a PaO_2 between 60 and 100 mm Hg, although one study defined it as a PaO_2 of 60–299 mm Hg (11). Timing of initial PaO_2 measure-

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 1. Outcomes Associated with Exposure to Hyperoxia in Patients with Traumatic Brain Injury

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Hyperoxia Exposure	Definition of the Reference Group	Primary Outcome in Exposed Group (Author Defined)
Alali, 2020 (10)	417	Secondary analysis of phase III RCT, COBRIT	> 18 yo, nonpenetrating TBI, initial GCS < 8, AIS > 3, GCS motor other than 6, admitted to level I trauma center	PaO_2 > 100, 150, 200, 250, 300, 350 mm Hg	Physiological range defined as PaO_2 80–100 mm Hg	GOSE score at 6 mo after TBI; better functional outcomes in the following groups: PaO_2 150–250 mm Hg; favoring mild hyperoxia
Ó Briain, 2018 (11)	24,148	Retrospective cohort study	> 17 yo, mechanical ventilation, admitted to ICUs in Australia and New Zealand	PaO_2 > 299 mm Hg, in the first 24 h of ICU admission	Hypoxia PaO_2 < 60 mm Hg, normoxia PaO_2 60–299 mm Hg	In-hospital mortality; no statistically significant difference in early exposure to hyperoxia compared with normoxia.
Brenner, 2012 (12)	1547	Retrospective cohort study	Patients with severe TBI (head AIS ≥ 3) who survived > 12 h after admission; 07/2002–07/2007; admitted to level I trauma center	PaO_2 > 200 mm Hg within the first 24 h	PaO_2 < 100 mm Hg and PaO_2 100–200 mm Hg	Higher rates of in hospital mortality in the hyperoxia group compared with normoxia group. OR 1.50; 95% CI 1.15–1.97
Davis, 2009 (13)	3420	Retrospective cohort study	Moderate to severe TBI (AIS ≥ 3), San Diego Trauma registry	Patients stratified by arrival PaO_2 value in 50-mm Hg increments	Not applicable	In-hospital mortality; PaO_2 110–487 mm Hg: optimal range for increased survival compared with other groups. Extreme hyperoxemia defined as PaO_2 > 487 mm Hg is detrimental
Vujanović Popović, 2014 (14)	49	Retrospective chart review	Isolated TBI, underwent ETI using the RSI method, prehospital setting in Slovenia	PaO_2 > 200 mm Hg	Hypoxia PaO_2 < 100 mm Hg, normoxia PaO_2 100–200 mm Hg	In-hospital mortality (24-h, 48-h survival); oxygenation status had no significant impact on 24-h and 48-h survival

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 1. (*continued*)

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Hyperoxia Exposure	Definition of the Reference Group	Primary Outcome in Exposed Group (Author Defined)
Rincon, 2014 (15)	1212	Retrospective multicenter cohort study	> 17 yo, ventilated patients with TBI admitted to a U.S. ICU, ABGs within 24 h of admission, 2003–2008	$PaO_2 \geq 300$ mm Hg within 24 h of ICU admission	Hypoxia PaO_2 < 60 mm Hg, normoxia not classified as hyperoxia or hypoxia	In-hospital case mortality; exposure to hyperoxia associated with higher in-hospital case fatality (adjusted OR 1.5; 95% CI 1.02–2.4; $p = 0.04$)
Taher, 2016 (16)	68	Randomized controlled double-blind clinical trial	18–65 yo; < 6 h since the accident; hemodynamic stability; GCS between 3 and 8, admitted to ED of Besat hospital in Hamadan (Iran)	80% FiO_2	50% FiO_2	GOS at discharge; GOS scores of patients treated with 80% oxygen were better than those with 50% oxygen ($p = 0.024$)
Tolias, 2004 (17)	164	Prospective historical cohort-matched study	> 16 yo; severe TBI; admitted to the neuro-ICU after intubation and ventilation; at least one reactive pupil and no chest injury or respiratory compromise or illness; microdialysis monitoring; ICP monitoring	100% FiO_2 for 24 h	No intervention no increase FiO_2	Biochemical markers in the microdialysate fluid from the brain; Increased glucose levels; decreased glutamate and lactate levels; reduced lactate/glucose and lactate/pyruvate
Weeden, 2020 (18)	3699	Retrospective multicenter cohort study	> 17 yo; had a primary APACHE III-J code of head injury or multitrauma; 1/2005–12/2017, mechanically ventilated; ICUs in Victorian hospitals	$PaO_2 \geq 300$ mm Hg	Hypoxia PaO_2 < 60 mm Hg, normoxia PaO_2 60–299 mm Hg	GOSE < 5 at 6 mo; no significant difference

ABG = arterial blood gas; AIS = Abbreviated Injury Scale; APACHE = Acute Physiology and Chronic Health Evaluation; COBRIT = Citicoline Brain Injury Treatment; ED = emergency department; ETI = endotracheal intubation; FiO_2 = fraction of inspired oxygen; GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale; GOSE = Glasgow Outcome Scale-Extended; ICU = intensive care unit; ICP = intracranial pressure; ICU = intensive care unit; OR = odds ratio; PaO_2 = partial pressure of oxygen; RCT = randomized controlled trial; RSI = rapid sequence intubation; TBI = traumatic brain injury; yo = years old.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 2. Outcomes Associated with Exposure to Hyperoxia in Patients with Cardiac Arrest

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Hyperoxia Exposure	Definition of the Reference Group	Primary Outcome in Exposed Group
Elmer, 2015 (19)	184	Retrospective cohort study	10/2008–04/2010; patients successfully resuscitated from CA and were both alive and mechanically ventilated for more than 24 h after ROSC	Severe hyperoxia: $PaO_2 \geq 300$ mm Hg; moderate hyperoxia: PaO_2 101–299 mm Hg	PaO_2 60–100 mm Hg	Lower odds of survival with each additional hour of exposure to severe hyperoxia, OR 0.84 (95% CI 0.72–0.98) No statistical difference in the moderate hyperoxia group, OR 1.01 (95% CI 0.96–1.05)
Elmer, 2015 (20)	170	Retrospective cohort study	10/2008–04/2010; CA survivors at ROSC, mechanically ventilated for at least 24 h after ROSC; both in- and out-of-hospital CA patients	AUC of the FiO_2 (FiO_2AUC)	—	No statistically significant change with increase in FiO_2AUC, OR 0.93 (95% CI 0.86-1.02) Lower odds of survival with increased exposure to hyperoxia, OR 0.90 (95% CI 0.82–0.98)
Jakkula, 2018 (21)	120	Prospective randomized pilot trial	18–80 yo, resuscitated from witnessed CA with VF or VT as initial rhythm, ROSC 10–45 min from the onset of CA; confirmed or suspected cardiac origin of the arrest; mechanical ventilation on ICU arrival; markedly impaired level of consciousness defined as no response to verbal commands and GCS motor score < 5 (withdrawal to painful stimuli at best); deferred consent from next of kin possible or likely; active intensive care and TTM initiated	PaO_2 of 150–190 mm Hg (20–25 kPa); high-normal $PaCO_2$ 43.5–45 mm Hg (5.8–6.0 kPa)	Normoxia (PaO_2 75–113 mm Hg) (10–15 kPa) and low-normal $PaCO_2$ 34–35 mm Hg (4.5–4.7 kPa)	Median NSE concentration at 48 h was 22.5 μg/L (IQR 14.2–34.9 μg/L) in the high-normal $PaCO_2$ group, $p = 0.400$; and 20.6 μg/L (IQR 14.2–34.9 μg/L) in the moderate hyperoxia group, $p = 0.594$).

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 2. (*continued*)

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Hyperoxia Exposure	Definition of the Reference Group	Primary Outcome in Exposed Group
McKenzie, 2021 (22)	491	Retrospective multicenter cohort study	$\geq$ 18 yo, with out-of-hospital CA of presumed medical etiology, received mechanical ventilation on admission to the ICU	Severely hyperoxemic, PaO_2 > 180 mm Hg	Mild to moderate hyperoxemia at PaO_2 100–180 mm Hg	Compared with the reference group of those with PaO_2 100–180 mm Hg, normoxemia (aOR 0.50; 95% CI 0.30 –0.84) and severe hyperoxemia (aOR 0.41; 95% CI 0.18 –0.92) were both associated with a reduced odd of STHD
Roberts, 2018 (23)	280	Prospective multicenter protocol-directed cohort study	7/2013–3/2017; $\geq$ 18 yo; CA; mechanical ventilation and targeted temperature management after ROSC	PaO_2 > 300 mm Hg during the initial 6 h after ROSC	Not hyperoxia ($PaO_2 \leq$ 300 mm Hg)	Hyperoxia associated with poor neurologic function (relative risk 1.23; 95% CI 1.11–1.35).
Thomas, 2019 (24)	35	Prospective controlled trial, cluster randomized (RCT)	> 6 mo; seen by a recruited study paramedic; underwent active resuscitation	100% oxygen for 1 h after ROSC	Titrated oxygen (targeted at 94–98% oxygen saturations)	3 of 17 (18%) in 100% oxygen group vs. 10 of 18 (55%) in titrated oxygen group

aOR = adjusted odds ratio; AUC = area under the curve; CA = cardiac arrest; GCS = Glasgow Coma Scale; IQR = interquartile range; NSE = neuron-specific enolase; OR = odds ratio; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; STHD = survival to hospital discharge; TTM = therapeutic temperature management; VF = ventricular fibrillation; VT = ventricular tachycardia; yo = years old.

Table 3. Outcomes Associated with Exposure to Hyperoxia in Patients with Other Disease Processes

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Exposure to Hyperoxia	Definition of the Reference Group	Primary Outcome in Exposed Group (Author Defined)
Duclos, 2021 (25)	424	Retrospective cohort	Chest AIS $>$ 2; ISS $>$ 15	Scaled by severity of average PaO_2: severe ($\geq$ 200 mm Hg), moderate ($\geq$ 150 and $<$ 200 mm Hg), and mild ($\geq$ 100 and $<$ 200 mm Hg)	PaO_2 of 60–100 mm Hg	Hyperoxemia was not associated with more complications, including incidence of HAP, ARDS, or death at 28 days
Russell, 2017(26)	472	Retrospective cohort	Admitted to ICU for at least 2 days	Maximum PaO_2 in first 24 h of admission	None	No association between increased PaO_2 within 24 h of ICU admission and in-hospital mortality In addition, there was no association between increased PaO_2 and mortality in the subgroup of patients with head trauma
Yamamoto, 2021 (27)	240	Post-hoc analysis of a prospective observational study	Inclusion: ISS $\geq$ 16, transported from scene	$PaO_2 \geq$ 300 mm Hg	Not hyperoxia ($PaO_2 <$ 300 mm Hg)	Hyperoxemia was associated with prolonged ICU stay; however, after inverse probability of treatment weighting analysis, there was only an association between hyperoxemia and prolonged ICU stay in patients who were not intubated in the ED, there was no such association in patients intubated in ED

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

Table 3. (*continued*)

First Author, Year	Sample Size	Study Design	Inclusion Criteria	Definition of Exposure to Hyperoxia	Definition of the Reference Group	Primary Outcome in Exposed Group (Author Defined)
Rincon, 2014 (15)	2894	Retrospective cohort	> 17 yo; ventilated patients with a primary diagnosis of acute ischemic stroke, aneurysmal subarachnoid hemorrhage, and intracerebral hemorrhage, consecutively admitted to a U.S. ICU	$PaO_2 \geq 300$ mm Hg	Normoxia (PaO_2 of 60–299 mm Hg) or hypoxia ($PaO_2 <$ 60 mm Hg)	Hyperoxia was an independent predictor of in-hospital mortality
Jouffroy, 2019 (28)	49	Retrospective observational	> 18 yo, meeting septic shock criteria per Surviving Sepsis campaign guidelines, subjected to assisted mechanical ventilation prior to admission	Categorized in 3 levels: 70 mm Hg $< PaO_2 <$ 100 mm Hg, 100 mm Hg $< PaO_2 <$ 150 mm Hg, and $PaO_2 >$ 150 mm Hg	70 mm Hg $< PaO_2 <$ 100 mm Hg; 100 mm Hg $< PaO_2 <$ 150 mm Hg	Elevated PaO_2 at ICU admission was associated with increased mortality at day 28
Asfar, 2017 (29)	442	Randomized controlled trial	> 18 yo, mechanical ventilation, septic shock refractory to fluid resuscitation requiring pressors	Exposure conditions of an FiO_2 of 1.0 for 24 h	Mechanical ventilation with FiO_2 set to achieve an arterial hemoglobin oxygen saturation between 88% and 95%	There was an overall increased mortality observed in the hyperoxia group, however, there was no statistically significant difference in 28-day or 90-day mortality between groups
Page, 2018 (30)	688	Observational cohort	Age $\geq$ 18 y, mechanical ventilation via an endotracheal tube; normoxia (PaO_2 of 60–120 mm Hg) on d1 of ICU admission	$PaO_2 >$ 120 mm Hg	Normoxia (PaO_2 60–120 mm Hg)	Patients with ED hyperoxia had greater hospital mortality ED hyperoxia was an independent predictor of hospital mortality

AIS = Abbreviated Injury Scale; ARDS = acute respiratory distress syndrome; ED = emergency department; FiO_2 = fraction of inspired oxygen; HAP = hospital-acquired pneumonia; ICU = intensive care unit; ISS = Injury Severity Score; PaO_2 = partial pressure of oxygen; yo = years old.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

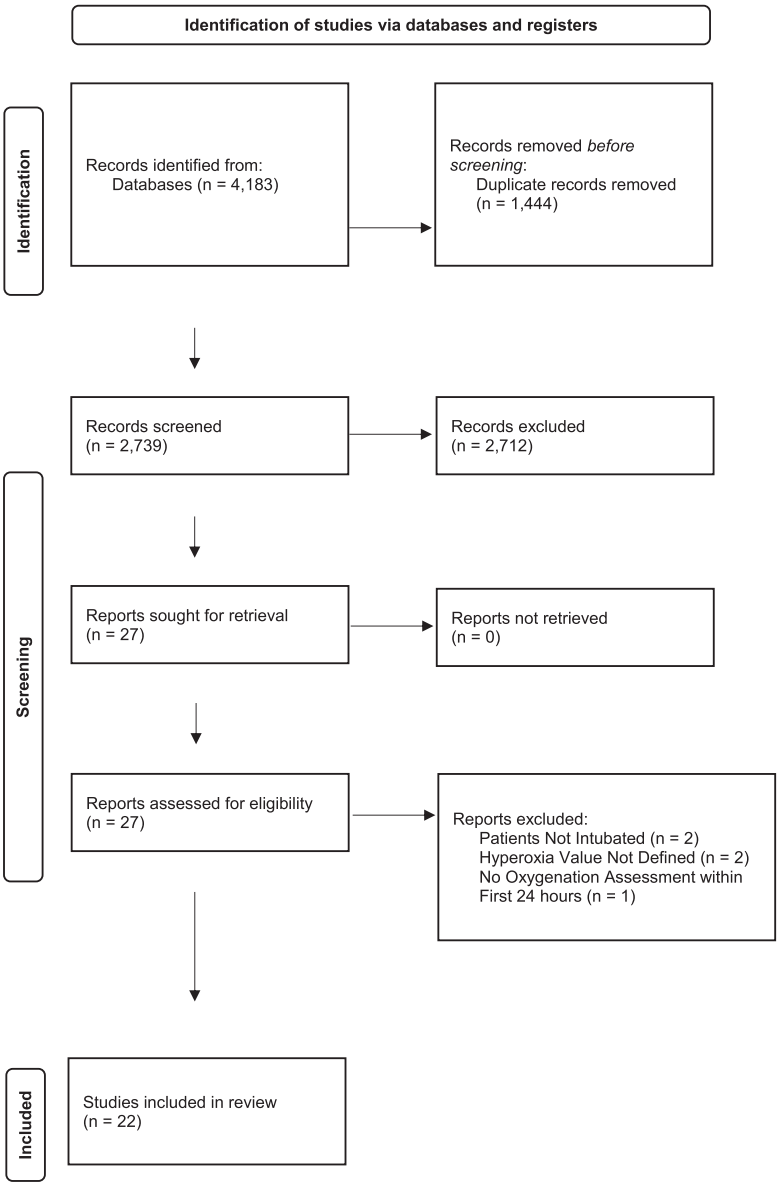

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

ment was also variable, including immediately on hospital arrival, ICU arrival, or at some point within the first 24 h.

Most studies examined in-hospital mortality as the primary outcome, although a few used Glasgow Outcome Scale (GOS) and other functional outcome scores. Taher et al. compared GOS at discharge and Alali et al. and Weeden et al. analyzed GOS 6 months after injury (10,16,18).

As demonstrated in Table 1, four studies observed favorable mortality or functional outcomes among patients with TBI exposed to early hyperoxia (10,13,16,17), three studies found no significant difference based on oxygen exposure (11,14,18), and three studies observed higher in-hospital mortality in patients exposed to early hyperoxia (12,13,15).

Cardiac Arrest

Six publications examined early hyperoxia exposure in patients after cardiac arrest (Table 2) (19–24). Most studies included patients 18 years and older, successfully resuscitated from cardiac arrest, survived to ICU admission, and mechanically ventilated on ICU arrival. Most of the patients were male and shared similar characteristics across the six articles (19–24).

Each publication defined hyperoxia uniquely; PaO_2 cutoff levels ranged from > 150 mm Hg to >300 mm Hg (19,21–23). Thomas et al. defined hyperoxia exposure as ventilation with 100% FiO_2 for the first hour after return of spontaneous circulation (ROSC) (24). Elmer et al.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

reported oxygen exposure as the area under the curve (AUC) of the FiO_2 during the 24 h after ROSC (20). Although similarly heterogeneous, the reference group was exposed to less oxygen than the hyperoxia group in all studies.

The studies varied greatly in the timing of the oxygen exposure quantification, including hourly PaO_2 measurements during the first 24 h after ROSC, calculating the AUC from hourly FiO_2 recordings for the 24 h after ROSC, and monitoring the titration of oxygen saturation every 2 min for the hour after ROSC in the titrated oxygen group by paramedics (19,20,24).

The primary outcome examined in most studies was survival, either survival to hospital discharge or at 12 months. In the study conducted by Elmer et al., exposure to severe hyperoxia (defined by the authors as $PaO_2 \geq 300$ mm Hg) was associated with lower odds of survival per additional hour of exposure (adjusted odds ratio [aOR]; 95% CI 0.83 0.69–0.99) (19). Exposure to moderate hyperoxia (PaO_2 101–299 mm Hg) was not associated with this finding. Elmer et al. reported lower odds of survival in those exposed to higher amounts of oxygen, as defined by the AUC of the FiO_2 during the 24 h after ROSC (OR 0.90; 95% CI 0.82–0.98) (20). McKenzie et al. found that exposure to a $PaO_2 > 180$ mm Hg was associated with reduced odds of survival to hospital discharge (aOR 0.41; 95% CI 0.18–0.92) (22).

Thomas et al. examined survival to discharge in two exposure groups during the first hours post ROSC: 100% FiO_2 and 94–98% FiO_2 (24). Fewer patients survived in the group exposed to 100% FiO_2 (18% vs. 55%), although this was a small study, and this finding was not subjected to statistical testing (24). McKenzie et al. found that maintaining mild to moderate hyperoxemia (PaO_2 100–180 mm Hg) during the first 24 h after ROSC was associated with significantly higher 12-month survival compared with those exposed to normoxemia ($PaO_2 <$ 100 mm Hg) or severe hyperoxemia ($PaO_2 > 180$ mm Hg) (aOR 0.41; 95% CI, 0.18–0.92) (22).

Another outcome measured in multiple studies was neurologic function. Roberts et al. found that exposure to hyperoxia ($PaO_2 > 300$ mm Hg) was associated with poor neurologic function at hospital discharge (23). Elmer et al. reported that a higher AUC of FiO_2 was associated with worse Cerebral Performance Category (CPC) at hospital discharge (20). Interestingly, McKenzie et al. found that normoxemia ($PaO_2 < 100$ mm Hg) and severe hyperoxemia ($PaO_2 > 180$ mm Hg) were both associated with increased odds of CPC 1 or 2 at hospital discharge (22). In contrast, Elmer et al. reported no association between exposure to any levels of oxygen and CPC at hospital discharge when analysis was restricted to survivors (19). Jakkula et al. reported no difference in neurologic outcome at 6 months between those exposed to hyperoxia (PaO_2 150–190 mm Hg) and normoxia (PaO_2 75–113 mm Hg) (21).

Discussion

Overall, we observed few studies that described clinical outcomes after acute, severe hyperoxia exposure in the post-intubation phase. During abstract and full-text screening, many studies were excluded if they assessed oxygenation without PaO_2 or SpO_2 measurements within the first 24 h of admission. The selected studies in this review examined a wide variety of underlying disease processes. Of the 22 included publications, only 3 were randomized controlled trials (RCTs). Most were retrospective cohort studies, limiting the data quality and ability to control for bias and confounders.

Significant heterogeneity of oxygen exposure quantification exists. Most studies used the PaO_2 on ICU arrival, and others used the PaO_2 immediately after intubation, on hospital arrival, or the mean PaO_2 over the first 24 h. With variation in PaO_2 sampling time, studies may have missed severe hyperoxia exposure during the initial resuscitation. Many patients in the included studies were intubated prehospital. However, oxygenation in the prehospital setting is recorded via pulse oximetry, which does not quantify the magnitude of hyperoxia exposure when high FiO_2 is used. Some studies defined hyperoxia exposure by administration of elevated FiO_2. PaO_2 is the gold standard for arterial oxygenation, thereby limiting direct comparison of hyperoxia exposure (3).

This review includes studies with exposure variables that were hospital-focused (e.g., arrival to the ICU) rather than patient-focused (e.g., PaO_2 post intubation). This exacerbates differences in the heterogeneous treatment environments of the study sites, as the PaO_2 on ICU arrival in one study may indicate prehospital oxygenation, and in another study, it may represent hours of hyperoxia exposure in the ED. A linear relationship has been described between the duration of hyperoxia exposure and mortality, highlighting the need for standardized approaches of determining hyperoxia exposure (31). In a meta-analysis by Helmerhorst et al., the authors found that a hyperoxic first ABG measurement was more consistently associated with poor clinical outcomes than hyperoxic mean oxygenation levels (32).

A unique observational study conducted by Page et al. is worth mentioning because it examined the effect of brief hyperoxia exposure in the immediate post-intubation phase in a heterogeneous, undifferentiated ED population (30). The authors found that hyperoxia exposure was independently associated with higher in-hospital mortality (30). In post-hoc analysis, the authors stratified hyperoxia exposure by severity and found a dose response, although

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

this outcome was not statistically significant (30). This study design evaluates the effect of acute, short-term hyperoxia exposure and may serve as a template for future study.

Many studies on hyperoxia exposure in patients with TBI demonstrated inconclusive results and were more heterogeneous than the studies with patients with cardiac arrest. This may be attributed to an incomplete understanding of the brain's complex metabolism (12). The TBI studies included patients who had moderate to severe TBI, as defined by various injury severity scores. These criteria allow highly variable disease processes, like epidural hematoma or diffuse axonal injury, to be grouped together. Although patients who have severe brain injuries may have similar GCS scores, the underlying mechanism and probability of responding to an intervention vary. The nine TBI studies we reviewed varied considerably in their hyperoxia definitions. Davis et al. commented on the survival benefits in patients exposed to "mild to moderate" hyperoxia, defined as a PaO_2 between 110 and 487 mm Hg (13). This definition is not consistent with basic biologic and pharmacologic principles. Contrarily, Brenner et al. and Helmerhorst et al. defined $PaO_2 > 200$ mm Hg as their threshold for hyperoxia and "severe hyperoxia," respectively (12,31). Of the cohorts we described, TBI had the largest proportion of studies favoring hyperoxia exposure. Given the breadth of definitions of hyperoxia thresholds and mechanisms of injury, the outcomes of these studies may not be generalizable to all patients with TBI. Thus, studies including homogeneous types of TBI and precise depth and duration of hyperoxia exposure are needed.

Among the subpopulation with cardiac arrest, we observed a possible detrimental effect of hyperoxia exposure. Every study that measured mortality reported lower odds of survival to hospital discharge among patients exposed to hyperoxia. Most of the other studies had some signal of harm, and none described benefit. This is consistent with the results of the meta-analysis by Helmerhorst et al., which showed that in-hospital mortality was significantly higher in patients resuscitated from cardiac arrest exposed to higher levels of oxygen (32). Similarly, in the RCTs evaluated by Chu et al., the authors observed increased overall mortality after liberal oxygen exposure in patients resuscitated from cardiac arrest (7). The dose-dependent relationship between hyperoxia exposure and worsening clinical outcomes in patients with ROSC after cardiac arrest described by Elmer et al. further highlight the potential implications of severe hyperoxia exposure and the need to investigate the optimal duration patients should be treated with high FiO_2 after ROSC (19). Taken together, these results support the hypothesis that exposure to hyperoxia may be detrimental after resuscitation from cardiac arrest. Contrary to the TBI group, standard inclusion criteria make the population with cardiac arrest more homogeneous. Thus, the signal of harm of hyperoxia is more clearly suggested.

The variability observed in the primary outcomes between the disease subgroups may be because the effect of hyperoxia varies based on the underlying disease process and baseline patient characteristics. A consequence of hyperoxia is the production of reactive oxygen species (ROS) (33). Critically ill patients with poor organ perfusion have increased production of ROS. This is exacerbated by exposure to excess oxygen (34,35). The controversial effects of oxygen therapy are seen in the vasculature as well, where hyperoxemia leads to systemic vasoconstriction. Subsequently, patients who develop myocardial infarction exposed to excess oxygen have decreased heart rate, stroke volume, and cardiac output, paradoxically worsening systemic perfusion (34). In patients with TBI, low tissue oxygen tension may lead to localized cerebral ischemia. The administration of supraphysiologic doses of oxygen to patients with TBI has been shown to improve cerebral aerobic metabolism and reduce intracranial pressure and is thus hypothesized to improve neurologic outcomes (33,34). At the same time, cerebral vasoconstriction can lead to decreased cerebral blood flow, resulting in further neurologic damage in patients with hypoxic brain injuries (33).

The volume of critical care delivered in EDs is increasing steadily. However, ED and ICU capacity are unable to meet this demand, resulting in an estimated 1.3–8.8 h of ED boarding per intubated patient (1). Delays to ICU transfer are associated with increased hospital length of stay and mortality (36). Excess oxygen administration may be a factor when considering the implications of boarding. Internal data from our nine-hospital, regional health care system suggest we are not managing these patients optimally. Among 410 patients with normal oxygen extraction intubated in our EDs, more than one-half were placed on 100% FiO_2, similar to data reported by Page et al. (30,37). This review highlights the potential for serious harm that can occur with hyperoxia exposure in a wide variety of critically ill patients. It is critical to consider the potential for harm after hyperoxia exposure and optimize oxygen delivery and titration. Although the time a patient spends boarding in the ED may be short relative to their overall hospital stay, those crucial few hours after initial resuscitation may have long-term clinical impacts.

Limitations

There are several limitations to interpreting these data. We found marked heterogeneity in the included cohorts, even when the same disease process was examined. In addition, few studies evaluated the most accurate marker of hyperoxia, PaO_2 after intubation. Furthermore, the timing of sampling of the exposure was poorly defined, occurring

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

at variable times throughout the first 24 hours of admission and often in the ICU. It is unclear when most of the hyperoxia exposure occurred in these cohorts. More research similar to the Page et al. study would clarify the role of hyperoxia in the acute post-intubation phase in ED patients. In addition, as previous studies have noted, there are no clear and consistent values and techniques that define hyperoxia. This variability limits our ability to directly compare results, as one study's definition of *normoxia* may be another's definition of *hyperoxia*. Moreover, there is substantial variability in ED logistics, with some patients going from the field straight to the ICU, where they may be managed differently than patients boarding in the ED.

Conclusions

Acute hyperoxia remains inconsistently defined in the literature. Depth and duration of hyperoxia and clinically relevant outcomes should be standardized to allow systematic, generalizable examination of the effect of hyperoxia exposure in the acute, post-intubation phase. This review highlights the absence of actionable data to guide clinicians in managing mechanically ventilated patients in this phase. The limited existing data suggest the potential for harm with hyperoxia exposure, particularly among patients post-cardiac arrest. The increased volume of critically ill ED patients combined with longer boarding times emphasizes the need to better understand the potential harm of hyperoxia exposure and optimize oxygen delivery and titration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jemermed.2023.08.002.

Appendix

Hyperoxia Review Search Strategies: Databases and Strategies

.

Ovid MEDLINE ALL 1946 to May 28, 2021		
Date Searched	6/1/21	
Concept	Search String	Results
1	hyperoxia.ti,ab. OR hyperoxic.ti,ab. OR hyperoxemia.ti,ab. OR hyperoxaemia.ti,ab. OR Hyperoxia/ OR Oxygen/to OR Oxygen/ae OR Oxygen Inhalation Therapy/ae OR Hyperbaric Oxygenation/ae	14,962
2	intubat*.ti,ab. OR (mechanical* ADJ2 ventilat*).ti,ab. OR artificial respirat*.ti,ab. OR supplemental oxygen.ti,ab. OR Intubation, Intratracheal/ OR Respiration, Artificial/ OR Oxygen Inhalation Therapy/	166,886
AND	1 AND 2	2664
Limits	NOT ((exp Adolescent/ OR exp Child/ OR exp Infant/) NOT exp Adult/) NOT (exp Animals/ NOT exp Humans/) NOT (Address.pt OR Comment.pt OR Editorial.pt OR Letter.pt OR News.pt)	
Total		1200
Ovid Embase Classic+Embase 1947 to 2021 May 28		
Date Searched	6/1/21	
Concept	Search String	Results

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

. (*continued*)

1	hyperoxia.ti,ab. OR hyperoxic.ti,ab. OR hyperoxemia.ti,ab. OR hyperoxaemia.ti,ab. OR Hyperoxia/ OR hyperoxia-induced lung injury/ OR Oxygen/ae OR Oxygen Toxicity OR Oxygen Therapy/ae	18,445
2	intubat*.ti,ab. OR (mechanical* ADJ2 ventilat*).ti,ab. OR artificial respirat*.ti,ab. OR supplemental oxygen.ti,ab. OR Respiratory Tract Intubation/ OR Endotracheal Intubation/ OR Endobronchial Intubation/ OR Rapid Sequence Induction/ OR Nasotracheal Intubation/ OR Artificial Ventilation/ OR Oxygen Therapy/	311,845
AND	1 AND 2	3203
Limits	NOT ((exp Juvenile OR exp Adolescent/ OR exp Child/ OR exp Infant/) NOT exp Adult/) NOT (exp Animal/ NOT exp Human/) NOT (Conference.pt OR Conference Abstract.pt OR Conference Paper.pt OR Conference Review.pt OR Editorial.pt OR Letter.pt)	
Total		1353

Ovid Cochrane Central Register of Controlled Trials April 2021
Date Searched 6/1/21

Concept	Search String	Results
1	hyperoxia.ti,ab. OR hyperoxic.ti,ab. OR hyperoxemia.ti,ab. OR hyperoxaemia.ti,ab. OR Hyperoxia/ OR Oxygen/to OR Oxygen/ae OR Oxygen Inhalation Therapy/ae OR Hyperbaric Oxygenation/ae	836
2	intubat*.ti,ab. OR (mechanical* ADJ2 ventilat*).ti,ab. OR artificial respirat*.ti,ab. OR supplemental oxygen.ti,ab. OR Intubation, Intratracheal/ OR Respiration, Artificial/ OR Oxygen Inhalation Therapy/	31,459
AND	1 AND 2	177
Limits	NOT ((exp Adolescent/ OR exp Child/ OR exp Infant/) NOT exp Adult/) / NOT (exp Animals/ NOT exp Humans/)	
Total		157

Ovid Cochrane Database of Systematic Reviews 2005 to May 26, 2021
Date Searched 6/1/21

Concept	Search String	Results

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

. (*continued*)

1	hyperoxia.ti,ab. OR hyperoxic.ti,ab. OR hyperoxemia.ti,ab. OR hyperoxaemia.ti,ab.	2
2	intubat*.ti,ab. OR (mechanical* ADJ2 ventilat*).ti,ab. OR artificial respirat*.ti,ab. OR supplemental oxygen.ti,ab.	287
AND	1 AND 2	2
Limits	None	
Total		2

Web of Science Core Collection (Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, ESCI) 1970-2021 (May 31)
Date Searched 6/1/21

Concept	Search String	Results
1	hyperoxia OR hyperoxic OR hyperoxemia OR hyperoxaemia	12,487
2	intubat* OR (mechanical* NEAR/2 ventilat*) OR artificial respirat* OR supplemental oxygen	117,795
AND	1 AND 2	1060
Limits	NOT (Editorial Material OR Proceedings Paper OR Meeting Abstract OR Letter)	
Total		968

Cumulative Index to Nursing and Allied Health Literature via EBSCOhost
Date Searched 6/1/21

Concept	Search String	Results
1	TI (hyperoxia OR hyperoxic OR hyperoxemia OR hyperoxaemia) OR AB (hyperoxia OR hyperoxic OR hyperoxemia OR hyperoxaemia) OR (MH "Hyperoxia") OR (MH "Oxygen/PO") OR (MH "Oxygen/AE") OR (MH "Oxygen Therapy/AE") OR (MH "Hyperbaric Oxygenation/AE")	1965
2	TI (intubat* OR (mechanical* N2 ventilat*) OR artificial respirat* OR supplemental oxygen) OR AB (intubat* OR (mechanical* N2 ventilat*) OR artificial respirat* OR supplemental oxygen) OR (MH "Intubation, Intratracheal") OR (MH "Intubation, Retrograde") OR (MH "Rapid Sequence Induction and Intubation") OR (MH "Respiration, Artificial") OR (MH "Oxygen Therapy")	58,626
AND	1 AND 2	829

(*continued on next page*)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

. (*continued*)

Limits	NOT ((MH "Adolescence+" OR MH "Child+" OR MH "Infant"+) NOT MH "Adult+") NOT (ZT "commentary") or (ZT "conference proceeding") or (ZT "editorial") or (ZT "letter") or (ZT "proceedings")	
Total		492

References

1. Mohr NM, Wessman BT, Bassin B, et al. Boarding of critically ill patients in the emergency department. Crit Care Med 2020;48:1180–7.
2. Winters ME, Hu K, Martinez JP, Mallemat H, Brady WJ. The critical care literature 2021. Am J Emerg Med 2023;63:12–21.
3. Rachmale S, Li G, Wilson G, Malinchoc M, Gajic O. Practice of excessive F(IO(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. Respir Care 2012;57:1887–93.
4. Helmerhorst HJF, Schouten LRA, Wagenaar GTM, et al. Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. Intensive Care Med Exp 2017;5:27.
5. Fracica PJ, Knapp MJ, Piantadosi CA, et al. Responses of baboons to prolonged hyperoxia: physiology and qualitative pathology. J Appl Physiol (1985) 1991;71:2352–62.
6. Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J 2009;158:371–7.
7. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018;391:1693–705.
8. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med 2018;169:467–73.
9. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev 2016;5:210.
10. Alali AS, Temkin N, Vavilala MS, et al. Matching early arterial oxygenation to long-term outcome in severe traumatic brain injury: target values. J Neurosurg 2020;132:537–44.
11. Ó Briain D, Nickson C, Pilcher DV, Udy AA. Early hyperoxia in patients with traumatic brain injury admitted to intensive care in Australia and New Zealand: A retrospective multicenter cohort study. Neurocrit Care 2018;29:443–51.
12. 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.
13. 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.
14. Vujanovic´Popovic´ V, Borovnik Lesjak V, Pelcl T, Strnad M. Impact of pre-hospital oxygenation and ventilation status on outcome in patients with isolated severe traumatic brain injury. Signa Vitae 2014;9:42–6.
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;85:799–805.
16. Taher A, Pilehvari Z, Poorolajal J, Aghajanloo M. Effects of normobaric hyperoxia in traumatic brain injury: a randomized controlled clinical trial. Trauma Mon 2016;21:e26772. doi:10.5812/traumamon.26772.
17. 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. doi:10.3171/jns.2004.101.3.0435.
18. Weeden M, Bailey M, Gabbe B, Pilcher D, Bellomo R, Udy A. Functional outcomes in patients admitted to the intensive care unit with traumatic brain injury and exposed to hyperoxia: a retrospective multicentre cohort study. Neurocrit Care 2020;34:441–8.
19. Elmer J, Scutella M, Pullalarevu R, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med 2015;41:49–57.
20. Elmer J, Wang B, Melhem S, et al. Exposure to high concentrations of inspired oxygen does not worsen lung injury after cardiac arrest. Crit Care 2015;19:105.
21. Jakkula P, Reinikainen M, Hästbacka J, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 2018;44:2112–21.
22. McKenzie N, Finn J, Dobb G, et al. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: a multicentre observational study. Resuscitation 2021;158:130–8.
23. Roberts BW, Kilgannon JH, Hunter BR, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability. Circulation 2018;137:2114–24.
24. Thomas M, Voss S, Benger J, Kirby K, Nolan JP. Cluster randomised comparison of the effectiveness of 100% oxygen versus titrated oxygen in patients with a sustained return of spontaneous circulation following out of hospital cardiac arrest: a feasibility study. PROXY: Post ROSC OXYgenation study. BMC Emerg Med 2019;19:16.
25. Duclos G, Rivory A, Rességuier N, et al. Effect of early hyperoxemia on the outcome in servere blunt chest trauma: A propensity score-based analysis of a single-center retrospective cohort. J Crit Care 2021;63:179–86.
26. Russell DW, Janz DR, Emerson WL, et al. Early exposure to hyperoxia and mortality in critically ill patients with severe traumatic injuries. BMC Pulm Med 2017;17:29.
27. Yamamoto R, Fujishima S, Sasaki J, et al. Hyperoxemia during resuscitation of trauma patients and increased intensive care unit length of stay: Inverse probability of treatment weighting analysis. World J Emerg Surg 2021;16(1):19.
28. Jouffroy R, Saade A, Saint Martin LC, Philippe P, Carli P, Vivien B. Prognosis value of partial arterial oxygen pressure in patients with septic shock subjected to pre-hospital invasive ventilation. Am J Emerg Med 2019;37:56–60.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

29. Asfar P, Schortgen F, Boisramé-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): A two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med 2017;5:180–90.
30. Page D, Ablordeppey E, Wessman BT, et al. Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study. Crit Care 2018;22:9.
31. Helmerhorst HJF, Arts DL, Schultz MJ, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. Crit Care Med 2017;45:187–95.
32. Helmerhorst HJF, Roos-Blom M, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies. Crit Care Med 2015;43:1508–19.
33. Lång M, Skrifvars MB, Siironen J, et al. A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress. Acta Anaesthesiol Scand 2018;62:801–10.
34. Damiani E, Donati A, Girardis M. Oxygen in the critically ill: friend or foe? Curr Opin Anaesthesiol 2018;31:129–35.
35. Huang D, Fang F, Xu F. Hyperoxia induces inflammation and regulates cytokine production in alveolar epithelium through TLR2/4-NF-κB-dependent mechanism. Eur Rev Med Pharmacol Sci 2016;20:1399–410.
36. Chalfin D, Trzeciak S, Likourezos A, Baumann B, Dellinger R. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med 2007;35:1477–83.
37. Verwiel C, Drescher G, Lawrynowicz M, et al. Low tidal volume ventilation and hyperoxia use among intubated adults with normal oxygenation. Acad Emerg Med 2023;30:77.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en diciembre 07, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.