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Newer Horizons in Human Excellence

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Article

Potential Harm of Hyperoxia in Children: A Narrative Review

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Abstract:

Background: Hyperoxia is common in pediatric critical care, yet its harmful effects remain underappreciated. This review combines clinical, physiologic, and molecular evidence showing that excessive oxygen exposure causes a range of lung and systemic injuries.

Methods: A structured literature search was performed in PubMed, Scopus, and Embase. Articles were selected to represent mechanistic, translational, and clinical evidence across relevant pediatric populations. The initial search strategy yielded 252 articles; 194 studies were excluded after initial screening. The remaining studies underwent independent full-text review and data extraction.

Pathophysiology: High FiO_2 leads to oxidative stress, damage to alveolar epithelial and endothelial cells, increased reactive oxygen species, release of inflammatory cytokines, changes in gene expression, and disruption of the alveolar-capillary barrier. Hyperoxia contributes to atelectasis, reduced lung compliance, decreases in vital capacity and diffusing capacity, and, with prolonged exposure, diffuse pneumonitis. Beyond the lungs, hyperoxia impairs immune regulation, gastrointestinal integrity, and nervous system development.

Results: Clinical research shows mixed results across different populations, but severe or sustained hyperoxemia is consistently linked to higher morbidity and mortality in critically ill children, those on ECMO, and certain neonatal and trauma groups. Studies in pediatric cardiac arrest and traumatic brain injury highlight the complex relationship between oxygen levels and neurologic outcomes, with hypoxia showing the strongest link to death. Advances like automated, closed-loop FiO_2 controllers show promise for optimizing oxygen delivery and reducing exposure to harmful extremes. Emerging molecular therapies, including growth factor modulation, antioxidants, and stem-cell-based treatments, may further reduce oxygen-related injury.

Conclusion: Overall, the evidence underscores the importance of carefully managing oxygen, a powerful drug with both lifesaving benefits and significant risks.

Keywords: Hyperoxia, hypoxia, critical care, pediatrics, oxygen toxicity

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Introduction

Oxygen is a common therapy to treat hypoxia in patients. Although vital to cell function, excessive exposure to oxygen can be detrimental.[1] While hyperbaric oxygen has specific clinical indications, excessive oxygen administration in most other conditions is unwarranted and often under-recognized.[2] While exposure to high levels of oxygen has been well-studied in animals, the clinical relevance of these findings may not be fully applicable to humans, as different species respond differently to high oxygen exposure.[3] In this review, we discuss results from human clinical and in vitro studies regarding the pulmonary effects of excessive oxygen administration.

Materials and Methods

A structured literature search was performed in PubMed, Scopus, and Embase using combinations of the terms: *hyperoxia, oxygen toxicity, pediatric, PICU, ECMO, traumatic brain injury, cardiac arrest, perioperative oxygen, COVID-19, automated FiO_2 control.* Articles were selected to represent mechanistic, translational, and clinical evidence across relevant pediatric populations. Because of marked heterogeneity in patient groups, exposures, and outcomes, formal systematic review methodology (PRISMA/PROSPERO) was not appropriate, and no meta-analysis was attempted. The initial search strategy yielded 252 articles, which were downloaded to Covidence for further screening by two reviewers (VB, JC). 194 studies were found irrelevant based on the inclusion and exclusion criteria. The remaining studies underwent independent full-text review and data extraction by the two reviewers (VB, JC) based on the inclusion and exclusion criteria listed here.

Inclusion Criteria: Case series, case control, cohort, Clinical trial: randomized or non-randomized, Meta-analysis with or without review. Population: Pediatric, neonate, Lab studies focused on hyperoxia. Intervention/exposure: Exposure to oxygen via mechanical or non-mechanical routes, Lab model of hyperoxia. Outcomes: Measures of cell, tissue, or organ dysfunction

Exclusion Criteria: Case report, Review without meta-analysis, Protocols. Population: Adults. Intervention/exposure: If no exposure to oxygen. Outcomes: If no outcome measures are studied

Definitions

The term hyperoxia is used interchangeably to describe both excessive oxygen administration as well as elevated partial pressure of oxygen (PaO_2) in the body. Excessive oxygen delivery and hyperoxemia can occur independently. In the setting of severe lung disease and limited diffusion, the PaO_2 may remain low or normal. Therefore, while pulmonary oxygen toxicity may occur with high oxygen delivery, hyperoxemia may not. On the other hand, any FiO_2 >21% has the potential to cause hyperoxemia and toxicity in organs exposed to elevated PaO_2.

Better terminology is necessary to characterize the appropriateness of oxygen therapy. *Excessive oxygen delivery* is the amount of administered oxygen that causes oxygen toxicity. *Hyperoxemia* refers to the presence of a supraphysiologic amount of oxygen in the blood, commonly defined by a PaO_2 threshold. The specific threshold of the fraction of inspired oxygen (FiO_2) above which toxicity occurs depends on the cell tolerance of the concentration and duration of oxygen to which it is exposed. Different cell types have different thresholds and variable responses.[4] Pulmonary oxygen toxicity is most common during normobaric oxygen therapy as airway and alveolar epithelial cells have the most exposure. A definitive threshold concentration or duration of oxygen therapy has not been found in humans. The commonly cited FiO_2 limit of 50-60% is largely based on animal and

in vitro studies.[5,6] A clear threshold PaO_2 that leads to end-organ injury has also not been identified. Many studies use PaO_2 thresholds beyond (e.g., 300 mm Hg) the upper limit of normal (approximately 100 mm Hg). Further studies are necessary to define the limits of oxygen therapy and toxicity in humans. Until more is known, setting FiO2 with target oxygen saturation and PaO_2 ranges (with upper limits) is most appropriate, with the acknowledgment that pulmonary toxicity can occur at high FiO_2 settings. Recently published pediatric guidelines in the management of patients with acute respiratory distress syndrome (ARDS) recommend maintaining a goal Spo_2 88% – 97% and < 92% in patients with severe ARDS with central venous oxygen saturation monitoring.[7]

Pathophysiology

Pathological changes occur with excessive oxygen delivery. In the 70s, multiple post-mortem case series attributed hyaline membrane formation and capillary proliferation in the child and adult population to high oxygen concentrations. Across both pediatric and adult patients—many without preexisting lung disease—post-mortem and clinical observations revealed diffuse alveolar damage after sustained oxygen therapy, regardless of delivery method or duration. Many patients in studies showing hyaline membrane disease had primary or secondary lung disease, required mechanical ventilation with high or unknown volumes or pressures, and received variable durations of oxygen supplementation. Collectively, these reports established an association between excessive FiO_2 and structural lung injury, though confounding factors such as infection and ventilation parameters make it difficult to attribute causality solely to oxygen toxicity.

In mechanically ventilated patients with acute lung injury (ALI), excessive oxygen delivery—e.g., FiO_2 >50% with SpO_2 >92%—is common and linked to adverse changes.[8] For example, FiO_2 1.0 increases intrapulmonary shunting due to derecruitment resulting from resorption atelectasis.[9] Pathological changes due to hyperoxia in mechanically ventilated patients are similar to those in patients who died with acute respiratory distress syndrome. Diffuse alveolar damage can occur after 48 hours of exposure to elevated oxygen levels.[10] During the exudative phase of ARDS, alveolar epithelial and endothelial cells show increased ROS-generating enzymes and apoptosis signaling (including NOX-linked pathways), consistent with concurrent oxidative stress and programmed cell death.[11] Even though oxygen toxicity cannot be identified as a cause of ALI, it can certainly contribute to similar clinical findings and exacerbate the disease process.

While many of the negative effects of excessive oxygen exposure on the lungs are well-documented, it is still unclear just how long it takes before this exposure causes significant risks. According to published reports, 6 hours of elevated oxygen increases reactive oxygen species and the elevation of inflammatory markers, a decrease in vital capacity occurs between ~24–77 hours on FiO_2 0.75–1.0, and tracheobronchitis occurs after ~6 hours on FiO_2 1.0 or ~12 hours on FiO_2 0.75.[12,13] Although the duration of hyperoxia in these studies is arbitrary, we can estimate that injury begins within hours of exposure and progresses over days, with a likely cumulative effect on lung architecture and mechanics.

Molecular Pathophysiology

Oxygen toxicity results from interference of reactive oxygen species (ROS) with normal cell structure and function and can occur with excessive oxygen exposure. ROS include superoxide (O_2-·), hydrogen peroxide (H_2O_2), and hydroxyl (·OH). They can form without excessive oxygen delivery and under physiologic conditions (e.g., infection). Normally, enzymes such as superoxide

dismutase and glutathione peroxidase inactivate reactive oxygen species. However, when antioxidant mechanisms are overwhelmed, such as in critical illness, oxygen toxicity can occur. ROS are produced by various cells through enzymes such as NADPH oxidase and xanthine oxidase.[11] Phagocytic cells (e.g., neutrophils, macrophages), pulmonary vascular endothelial cells, and alveolar epithelial cells have all been implicated in the production of ROS.[11,14] NADPH oxidase is an important source of ROS in pulmonary endothelial cells and alveolar epithelial cells.[11,14] The SphK1/S1P/Spns2 axis also drives hyperoxia-induced endothelial NOX2 activation and ROS generation.[15]

ROS cause cellular injury by altering gene expression, signaling pathways, and/or damaging DNA, protein, and lipids.[16] Cell signaling is altered to initiate protective mechanisms, such as maintaining mitochondrial integrity or triggering programmed cell death, during oxidative stress.[17] Increase in ATP production in human pulmonary endothelial cells and release into the extracellular environment leads to activation of receptors that signal changes in protein synthesis and glucose metabolism during periods of oxidative stress.[18] Enzymes involved with apoptosis increased in airway epithelial cells exposed to >95% oxygen in vitro for up to 72 hours. These enzymes induced cell death by affecting apoptotic signaling pathways.[19] Alveolar epithelial function is also affected by changes to signaling pathways that lead to cell death, evidenced by apoptotic and necrotic changes. Other signaling mechanisms can enhance the ROS response, possibly activating protective mechanisms. Activation of mitogen-activated protein kinases (MAPK) in human pulmonary endothelial cells occurred when exposed to 95% oxygen.[14] MAPKs, which are important signaling proteins, in turn alter signaling pathways that increased ROS production.

Altered gene expression in the lungs results in the synthesis of proteins that regulate detoxification, inflammation, cell proliferation, and cell death. Although these changes are initially adaptive—aimed at protecting cells from oxidative injury—they can paradoxically contribute to local damage through inflammation and cell loss, ultimately impairing lung function. In vitro studies have shown that exposing human pulmonary artery endothelial cells to 90% oxygen for 48–72 hours increases the expression of intercellular adhesion molecule-1 (ICAM-1), thereby enhancing neutrophil adherence.[20] Similarly, exposure to hyperoxia modulates the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, with IL-8 demonstrating the most consistent and pronounced increase. In alveolar macrophages isolated from bronchoalveolar lavage (BAL) fluid of children and exposed to 95% oxygen for 48 hours, IL-8 levels were significantly elevated. A comparable increase in IL-8 was also associated with enhanced polymorphonuclear leukocyte chemotaxis in adult cell models. Inflammatory activation also extends to TNF-α; its concentration rises under both LPS-stimulated and high-oxygen conditions, reaching statistically significant levels in macrophages exposed to 60–95% oxygen compared with normoxic (21%) conditions.[21] Additional genes implicated in *oxygen-induced injury include gasdermin D (GSDMD)*, which mediates pyroptotic cell death, and *connective tissue growth factor (CTGF)*, which promotes fibrotic and inflammatory pathways.[22,23]

Excessive oxygen leads to short and long-term damage. Alveolar macrophages release fibronectin and alveolar-macrophage-derived growth factors, which attract fibroblasts, causing chronic lung changes. Human lung fibroblasts exposed to 95% oxygen ROS increased RhoA activation.[24] RhoA is a small GTPase that regulates various cell functions, including the mediation of collagen-I synthesis and lung fibrosis in the setting of high oxygen.

While most studies investigating the molecular pathophysiology of hyperoxia have focused on cell signaling in the lungs (and, in the neonatal population, retinal tissues), there is also evidence of damage to various other organs including the brain, immune system, and gastrointestinal tract. Yis et al found that exposure of rat pups to 80% oxygen from birth to five days of life was associated with increased cell death in the developing brain as compared to 21% oxygen.[25] Additional studies

have shown impaired FoxP3+- regulated T cell generation and T cell autoreactivity in mice, increased secretory IgA (SIgA) from intestinal epithelial cells, and gut inflammation/dysbiosis via TLR-4, TNF, NF-*κB*, and Nrf2 pathway activation.[22,25,26]

Alveolar Cell Death & Damage to Alveolar-Capillary Barrier

ROS-induced changes in gene expression, signaling pathways, and damage to DNA, proteins, and lipid membranes can lead to cell death by apoptosis and/or necrosis. Many studies support apoptotic processes in cells exposed to high levels of oxygen Apoptosis was attenuated in the presence of vitamin E, an antioxidant. Evidence of necrosis was observed in alveolar epithelial cells, specifically in human lung adenocarcinoma cells A549, upon exposure to 95% oxygen. The term "necroptosis" has been proposed to encompass a dual mechanism of cell death. Simultaneous occurrence in different cells and/or sequential processes has been suggested. Injury to alveolar epithelial and endothelial cells compromises the alveolar-capillary barrier. This occurs independent of cellular inflammation when exposed to excessive oxygen.

Clinical Studies

Early studies dating back to the 1940s showed the effects of the delivery of high concentrations of oxygen to the lungs. A few studies isolated excessive oxygen exposure by including only healthy adults with no history of lung pathology and administering oxygen by noninvasive methods, thereby excluding any effects of positive-pressure ventilation. Later studies included mechanically ventilated lungs. Many of these studies did not provide details on ventilator management or explain the possible roles of barotrauma or volutrauma. Accurate conclusions cannot be made about the isolated effects of oxygen therapy, but the results indicate that caution is warranted when determining the level of FiO_2 to administer.

Hyperoxia Clinical Trials

Elevated oxygen levels, when employed clinically, can induce various pulmonary damages, ranging from tracheobronchitis to widespread alveolar injury. Tracheobronchitis, often attributable to diminished ciliary activity, represents among the earliest indicators of pulmonary oxygen toxicity. Patients may present with chest pain, cough, and dyspnea.13 For instance, in one study, the exposure to 95% oxygen via a non-rebreather mask for 15.5-18 hours resulted in chest pain in 9 of 14 patients.[27] Although the discomfort subsided following cessation of oxygen therapy, bronchoscopy revealed erythema in 6 patients, indicative of inflammation.

Further symptoms of pulmonary oxygen toxicity include alveolar atelectasis (both absorptive and obstructive), decreased lung compliance, reduced vital capacity, and diminished diffusing capacity.[28] A study involving eight aircrew subjected to high oxygen delivery and hypergravity associated oxygen exposure with atelectasis, with ultrasound indicating greater atelectasis following breathing 100% oxygen compared to 44.5% and 21% oxygen.[29] A decline in vital capacity was noted between 24 and 77 hours at FiO_2 0.75-1.0. Although limited, these studies suggest that oxygen levels of 50% or higher can provoke adverse clinical effects, with cellular damage likely initiating within hours, even if clinical signs manifest subsequently.

Extensive research has examined hyperoxia's impact on mortality across various populations. These are summarized below in Table 1.

Hyperoxia and Critically Ill Pediatric Patients

Hyperoxia is common in critically ill children at admission to a PICU and is associated with increased risk-adjusted mortality. The effect of hyperoxia on critically ill pediatric patients appears dose-dependent. Like the studies on cardiac arrest, it is consistently observed that hypoxia results in worse outcomes compared to hyperoxia. However, several studies have identified a link between hyperoxia and increased morbidity and mortality in critically ill children. Most pediatric research indicates that severe hyperoxia or hyperoxemia is associated with poorer outcomes, especially with longer or more frequent exposures to these conditions effects.[30-36.]The level of hyperoxia differs across studies, with Numa et al identifying a risk minimum around a PaO_2 of 100-200 mmHg, whereas Pelletier et al reported that harmful hyperoxia occurs over 450 mmHg in one study and between 250-400 mmHg in another.[37-39] **(Table 1)**

Table 1: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill ICU Populations

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
KAPADIA, 2013[40]	Neonates (24-34 Weeks Gestational Age); delivery room resuscitation	Prospective, RCT N = 88 (44 per group)	Limited oxygen strategy (LOX): incremental increase in FiO_2 from 21% to achieve the target SpO_2. High oxygen strategy (HOX): 100% FiO_2 initiated and adjusted every 30 seconds to meet the target SpO_2 of 85% to 94%.	LOX effectively resuscitated preterm neonates, decreased oxygen load by 50% (401 ± 151 vs 662 ± 249; P < .01), lowered ventilator days (3 [0-64] vs 8 [0-96]; P < .05), rescue HFOV, and BPD (7% vs 25%; P < .05). LOX group spent less time with SpO2 > 94% and developed less oxidative stress by 1 hour of life.
LILIEN, 2022[41]	Pediatric patient	Systematic review N = 27,555 11 studies pooled for meta-analysis (N = 23,204)	Variable definitions of hyperoxia, with studies determining hyperoxia as PaO2 values > 120mm Hg to > 300mm Hg.	Variability in mortality associated with hyperoxia across studies. Hyperoxia increased the odds of mortality (OR 1.59, 95% CI, 1.00-2.51).
RAMGOPAL, 2019[32]	Patients admitted to the pediatric ICU (age ranges < 30 days to ≤ 18 years) with PaO2 values collected at any point during admission	Retrospective cohort study N = 6,250	Severe hyperoxemia: PaO_2 ≥ 300mm Hg.	Severe hyperoxemia (dose-response relationship) is independently associated with in-hospital mortality. ([aOR], 1.78; 95% CI, 1.36-2.33; P < .001).
RAMGOPAL, 2020[33]	Pediatric patients admitted to the PICU with PaO_2 values obtained in the 6 hours prior to or after admission to the ICU	Single-center observational study N = 4,093	Hyperoxemia: PaO_2 ≥ 300mm Hg; Hypoxia: PaO2 < 60mm Hg.	Hypoxemia was associated with increased in-hospital mortality. Hyperoxemia overall is not associated with in-hospital mortality (aOR, 1.38; 95% CI, 0.98-1.93), except at extremes (PaO_2 ≥ 550 torr)

RAMAN, 2016[34]	Patients < 18 years admitted to ICU	Retrospective cohort study N = 7,410 patients	Hyperoxia: PaO_2 > 300 torr; Hypoxia: PaO_2 < 60 torr OR SpO_2 < 90%.	U-shaped association between admission PaO_2 and mortality. Hypoxia increased risk of death. OR 3.13 (95% CI, 1.79-5.48; p < 0.001) No increase in mortality with hyperoxia (OR, 1.15; 95% CI, 0.42-3.17; p = 0.77).
NUMA, 2018[37]	Pediatric patients ages 0 to 18 years admitted to ICU	Single-center retrospective analysis N = 1,447	Oxygenation values broken down by 50mm Hg increments for analysis. Hyperoxia defined as PaO_2 > 250mm Hg.	U-shaped relationship between mortality and admission PaO_2. Lowest mortality observed in PaO_2 of 101-150mm Hg and 151-200mm Hg. Highest mortality in the PaO2 > 350mm Hg and PaO_2 < 50mm Hg. Odds ratio for hyperoxia predicting death was 2.66 (p = 0.047).
VAN DER WAL, 2023[42]	Patients > 18 years with mechanical ventilation duration of at least 24 hours	Randomized multicenter trial N = 664 Stopped prematurely due to COVID-19 pandemic (only 664 of the planned 1,512 patients recruited)	Low oxygenation group: PaO_2 55-80mm Hg OR SpO_2 91-94%. High oxygenation group: PaO_2 110-150mm Hg OR SpO_2 96-100%.	No reduction in 28-day mortality with low oxygenation strategy compared to high oxygenation strategy.
BALCARCEL, 2022[31]	Patients < 18 years requiring mechanical ventilation within 3 days of admission	Retrospective, observational cohort study N = 5,406	Hypoxemia: SpO_2 < 90% at any point in the first 24 hours of mechanical ventilation. Cumulative Excess Oxygen Exposure (CEOE): mean hourly FiO_2 provided above 0.21 when the SpO_2 was ≥ 95% during the first 24 hours of mechanical ventilation.	Higher CEOE increased odds of in-hospital mortality (aOR, 1.7; 95% CI, 1.1-2.9), and MODS on day 7 (aOR, 3.9; 95% CI, 2.7-5.9). Hypoxemia-associated mortality and MODS were comparable to the highest CEOE group.
GEVA, 2023[36]	Patients aged 7 months to < 16 years admitted to the PICU and mechanically ventilated via endotracheal tube for at least 24 hours	Retrospective cross-sectional study N = 3,354	Hypoxia: SpO_2 reading < 90% at any point during the 24 hours of mechanical ventilation. Hyperoxia: Cumulative Excess Oxygen Exposure (CEOE): mean hourly FiO_2 provided above 0.21 when the SpO_2 was ≥ 95% during the first 24 hours of mechanical ventilation.	Higher CEOE quartiles were associated with greater mortality, but this finding was primarily in the highest quartile.

Abbreviations: Randomized control trial (RCT), fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), oxygen peripheral saturation (SpO_2), odds ratio (OR), intensive care unit (ICU), adjusted odds ratio (aOR), pediatric intensive care unit (PICU), high frequency oscillatory ventilation (HFOV), bronchopulmonary dysplasia (BPD), cumulative excess oxygen exposure (CEOE), multiorgan dysfunction syndrome (MODS)

Hyperoxia and Traumatic Brain Injury (TBI)

Numerous studies involving both adult and pediatric TBI patients suggest that hyperoxia might be neuroprotective. While some studies suggest improvement in biomarkers and reduced intracranial pressure across adult and pediatric patients. None of the studies demonstrated an association between hyperoxia and improvement in neurological outcomes. **(Table 2)**

Table 2: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill patients after trauma or a traumatic brain injury

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
BAEKGAARD, 2020[43]	Trauma patients > 17 years	Observational study using a multicenter, prospective trauma registry. N = 5,912	Hyperoxia: PaO2 ≥ 150 mmHg on admission	Univariate analysis showed higher in-hospital mortality for hyperoxemic patients compared to normoxemic patients. After propensity matching, significantly lower in-hospital mortality for hyperoxemic patients compared to normoxemic patients.
JEONG, 2018[44]	Patients > 16 years, who survived for at least 5 days after ED arrival	Observational cohort study N = 10,141 Exclusion: < 2 ABGs, maximum PaO2 < 60mm Hg, Died, transferred to ICU, or had complications within 5 days of ED arrival, hospital LOS > 90 days, unable to calculate AUC, acute MI	Area under the curve over 72 hours (AUC72) calculations using highest PaO_2, average PaO_2, and median PaO_2. Hyperoxemia: max PaO_2 > 137mm Hg, average PaO2 > 105mm Hg, median PaO_2 > 103, and AUC72 > 174mm Hg.	Significant correlations between all hyperoxemia variables with 90-day in-hospital mortality. After adjustment, only AUC_{72} was significantly associated with 90-day in-hospital mortality. (aOR 1.53 (95% CI 1.25 to 1.88; p<0.0001). AUC_{72} also associated with ICU transfer, end organ failure.
TOLIAS, 2004[45]	Patients > 16 years with severe TBI treated with normobaric hyperoxia (FiO2 1.0) for 24 hours, starting within 6 hours of admission	Prospective clinical trial N = 52 in treatment and N = 112 in matched control cohort	Hyperoxia: FiO_2 1.0 administration for 24 hours, started within 6 hours of admission.	Hyperoxia group: Improved biomarker profile and lower intracranial pressure.

NORTJE, 2008[46]	Patients > 15 years with TBI	Prospective clinical trial N = 11 patients	Cerebral microdialysis, brain tissue oximetry (PbO_2), and oxygen-15 positron emission tomography (150-PET) normoxia (FiO_2: 0.35 to 0.5) and repeated at hyperoxia (FiO_2: 0.6 to 0.8). PaO_2 at baseline: 99 +/-23; Hyperoxia PaO_2: 226 +/- 68	Hyperoxia increased the mean PbO_2 and reduced the lactate: pyruvate ratio.
FIGAJI, 2010[47]	Patients < 15 years with severe TBI	Prospective observational study 48 tests performed in 28 patients who underwent PbO_2 monitoring and an oxygen challenge test (temporary increase in FiO_2 for 15 minutes)	Pre- and post-test values (PbO_2, ICP, CPP, PaO_2, arterial saturation (SaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$)) measured	Linear increase in PbO_2 with normobaric hyperoxia. A greater PbO_2 response to PaO_2 change is associated with a worse outcome.
KETHARANATHAN, 2020[48]	Patients < 18 years with accidental severe TBI (GCS 8 or less)	Retrospective explorative study N = 71	Hyperoxia cutoffs: PaO_2 > 200mm Hg, > 250mm Hg, > 300mm Hg. Highest PaO_2 value for each individual patient in the first 24 hours of PICU admission used PaO_2 cumulative area under the curve (AUC); AUC value cutoffs: <2000 (physiological oxygen exposure), 2000-4000 (intermediate oxygen exposure), >4000 (high oxygen exposure)	Hyperoxia classification differed depending on PaO_2 cutoff vs AUC analysis. AUC better approximates physiological circumstances due to time and dose-dependent approach
TANG, 2024[49]	Patients < 18 years with severe accidental TBI (GCS 3-8)	Prospective institutional registry N = 98	First, highest, and area under the curve (AUC) PaO_2 in the first 24 hours of admission to the ICU were evaluated Hyperoxia: PaO2 > 300mm Hg.	Hyperoxia incidence 33% Hyperoxia not associated with unfavorable outcome after 6 months.

Abbreviations: Arterial partial pressure of oxygen (PaO2), emergency department (ED), arterial blood gas (ABG), emergency department (ED), length of stay (LOS), area under the curve (AUC), myocardial infarction (MI), area under the curve over 72 hours (AUC72), adjusted odds ratio (aOR), confidence interval (CI), traumatic brain injury (TBI), fraction of inspired oxygen (FiO2), brain tissue oximetry (PbO2), intracranial pressure (ICP), cerebral perfusion pressure (CPP) arterial oxygen saturation (SaO2), arterial partial pressure of carbon dioxide (PaCO2), Glasgow coma score (GCS)

Hyperoxia and Pediatric Cardiac Arrest

Multiple studies have examined the link between hyperoxia and outcomes following pediatric cardiac arrest. These are summarized below in Table 3. The smaller studies demonstrated no difference in outcomes in patients with hyperoxia (PaO_2 > 200 mmHg) in the first six hours[50]. The larger studies revealed worse outcomes associated with hypoxia and extremes of hyperoxia (PaO_2 > 600 mmHg), which the studies concluded were rarely observed.[51] These studies concluded that in the post cardiac arrest phase hypoxia is more critical than hyperoxia and associated with worse outcomes.

Table 3: Characteristics and Outcomes of Studies Assessing Hyperoxia in Critically Ill patients after cardiac arrest or requiring extracorporeal membrane oxygenation (ECMO)

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	OXYGENATION PARAMETER	STUDY FINDINGS
SZNYCER-TAUB, 2016[52]	Patients < 1 year undergoing cardiac surgery requiring postoperative VA ECMO	Retrospective chart review; N = 93	Hyperoxia: mean PaO_2 > 193 mm Hg in the first 48 hours of ECMO.	Total mortality~ 38%. Hyperoxia an independent risk factor for 30-day mortality. (p = 0.001) Hyperoxia is associated with the need for dialysis (p = 0.02).
BENNETT, 2013[50]	Pediatric patients aged 24 hours to 18 years who experienced cardiac arrest with return of circulation for ≥ 20 minutes	Retrospective cohort study; N = 195 cardiac arrest events were included in the study	Hyperoxia: defined as PaO_2 > 200 mm Hg in the first 6 hours post-cardiac arrest. Hypoxia: PaO_2 < 50mm Hg.	13% of patients maintained both normoxia and normoventilation. 10% of patients with both hyperoxia and hypoxia. No difference in outcomes (survival with good outcome 34% for hyperoxia compared to 42% with normoxia (p = 0.23)).
FERGUSON, 2012[51]	Patients < 16 years with cardiac arrest and ABG taken within 1 hour of PICU admission	Retrospective cohort study N = 1875 patients included in analysis	Hypoxia: PaO2 < 60 mm Hg; Hyperoxia: PaO2 ≥ 300 mm Hg.	Mortality 39%. Incidence (hypoxia 24%, hyperoxia 11%, normoxia 65%). Severe hypoxia increased the probability of death (OR 1.92; 95% CI, 1.80-2.21). Hyperoxia also increased risk of ICU mortality (OR 1.2; 95% CI 1.0-1.5). Increased risk with higher degrees of hyperoxia (mortality OR 1.12 per 100 mm Hg increase in PaO2). Optimal PaO2 after cardiac arrest: 60-75 mm Hg.
CASHEN, 2018[35]	Pediatric patients < 19 years treated with ECMO	Retrospective, secondary analysis N = 484	Hyperoxia: highest PaO_2 > 200 Torr during the first 48 hours on ECMO.	Hyperoxia associated with higher mortality and shorter durations of ECMO and ICU stays (167 [50.5%] vs 48 [31.4%]; p < 0.001. No functional status differences at discharge.
FRAZIER, 2024[53]	Patients ≤ 18 years receiving chest compressions during ICU stay	Embedded prospective observational study N = 284 Exposures: hypoxemia, hyperoxemia, or normoxemia based on the lowest PaO_2 within the first 24 hours post-arrest	Hypoxemia: PaO_2 < 60 mm Hg; Hyperoxemia: PaO2 ≥ 300 mm Hg; Normoxemia: PaO_2 between 60 mm Hg and 300 mm Hg	Hypoxemia group less likely to survive to hospital discharge (aRR 0.71; 95% CI 0.58-0.87).

Abbreviations: Veno-arterial extracorporeal membrane oxygenation (VA ECMO), arterial partial pressure of oxygen (PaO2), arterial blood gas (ABG), pediatric intensive care unit (PICU), intensive care unit (ICU), odds ratio (OR), adjusted risk ratio (aRR)

Hyperoxia in COVID-19

Hyperoxemia was common during the COVID-19 pandemic, especially among mechanically ventilated patients receiving prolonged high FiO_2.[54] Prospective and observational cohorts consistently showed a high prevalence of hyperoxemia and "excessive oxygen use" in COVID-19 ARDS populations. Outcome associations, however, have been inconsistent. In a single-center cohort of invasively ventilated patients, time spent in hyperoxemia (PaO_2 >100 mmHg) and combined hyperoxia–hyperoxemia (FiO_2 >0.60 with PaO_2 >100 mmHg) were independently linked to higher ICU mortality and increased ventilator-associated pneumonia.[55] Conversely, analysis of the multicenter PRoVENT-COVID study found no difference in 28-day, 90-day, or out of hospital mortality between hyperoxemic and normoxemic patients after matching, despite frequent early PaO_2 >90 mmHg.[54] Interventional evidence from the HOT-COVID randomized trial showed that targeting a lower PaO_2 (≈60 mmHg) was associated with more days alive without life support than targeting a higher PaO_2 (≈90 mmHg), supporting conservative oxygen strategies, even without a difference in mortality.[56] Overall, these data suggest that while hypoxemia remains the primary concern, sustained hyperoxemia offers no benefit and may cause harm, emphasizing the importance of early FiO_2 reduction in COVID-19 ARDS. There is currently a lack of specific pediatric data on hyperoxemia (e.g., elevated PaO_2 levels) and its effect on clinical outcomes in children with COVID-19. Current pediatric COVID-19 research mainly concentrates on respiratory support methods, predictors of severe disease, and managing hypoxemia, rather than the effects of prolonged high PaO_2 exposure.

Management Targets

Contemporary pediatric guidance emphasizes that oxygen should be titrated to avoid both hypoxemia and sustained hyperoxemia. The PALICC-2 recommendations for pediatric ARDS support targeting oxygenation ranges that achieve adequate delivery while minimizing FiO_2 exposure, using SpO_2 goals generally in the 92–97% range and prioritizing early FiO_2 reduction once targets are met.[7] In pediatric cardiac arrest care, international consensus recommends FiO_2 1.0 during active resuscitation, followed by prompt titration after return of spontaneous circulation to avoid extremes of oxygenation (goal SpO2 94 - 99%); post-ROSC management aims for near-normal oxygenation, avoiding hyperoxemia when arterial blood gases are available.[57] Across these settings, guidance consistently highlights frequent reassessment, use of arterial blood gas (ABG) confirmation when feasible, and avoidance of prolonged high FiO_2 in the absence of refractory hypoxemia, reflecting the principle that oxygen is a drug with both lifesaving benefits and potential toxicity.

Oxygen administration is similar to other drugs and must be titrated to achieve the desired effect. However, achieving the exact blood oxygen level is challenging. Adjusting FiO_2 during maintenance and weaning can be challenging, as even small changes in inspired oxygen can lead to unintended fluctuations in oxygen saturation. Proper titration is essential, but it's often hindered by factors such as staff experience and staffing levels, leading to significant variability in SpO_2 levels. Automated oxygen controllers can help reduce the risks associated with weaning from oxygen therapy. Automated oxygen controllers have successfully maintained oxygen saturation in target ranges in neonatal patients[58-65] and shown to be feasible for titration in adults with chronic obstructive pulmonary

disease (COPD). Neonatal studies compared manual FiO_2 adjustment with automated open and closed-loop FiO_2 control systems in neonates receiving both invasive and non-invasive oxygen support. The automated systems consistently demonstrated greater effectiveness in keeping oxygen levels within the target range. While neonatal studies did not consistently prove the prevention of acute hypoxia, they did show a decrease in the duration of prolonged hypoxemic and hyperoxemic episodes.[64] Neonatal patients using automated oxygen controllers were found to have much better compliance with normoxic target ranges with less time spent severely hyperoxic.[66] Additionally, these patients tended to have a shorter duration of mechanical ventilation compared to those not on automated oxygen controllers.[67] These studies are summarized in table 4.

Table 4: Table summarizing open and closed loop automated controllers in the neonatal and pediatric population.

AUTHOR, YEAR OF PUBLICATION	TARGET POPULATION	STUDY DESIGN, SAMPLE SIZE. (N)	STUDY FINDINGS
IR, 1979	Preterm neonates in the first week of life	Prospective clinical trial N=12 Automated control of FiO_2 to meet PaO_2 goals between 55mm Hg and 80mm Hg using an indwelling arterial electrode sensor connected to the ventilator.	PaO_2 outside target range 12.2% of the time during the automatic servo-control period compared to 27.6% in the manual-control period.
DUGDALE, 1988	Neonates with RDS	Prospective clinical trial N=7 A microcomputer-based closed-loop control system using the PaO_2 value from an indwelling umbilical artery electrode as input. Titration of oxygen. Duration 48 hours	Percentage of time for which the PaO_2 was within +/- 1 kPa of the chosen target value using a closed-loop PaO_2 regulator was 74.9 +/- 10.2% compared to 45.2 +/- 16.0% when using comparable manual control intervals
BHUTANI, 1992	Infants with BPD	Prospective clinical trial N=14 Adaptive adjustment of inspired oxygen (FIO2), based on a desired percent arterial hemoglobin saturation.	SpO_2 values within target range: 54% with standard protocol, 69% ($P < 0.01$) with bedside manual control and 81% ($P < 0.01$) with adaptive control. Fluctuations in SpO2 values and overshoots were less common with adaptive control.
SUN, 1997	Newborn infants requiring mechanical ventilation	Prospective clinical trial N=16 Open-loop computer control of inspired oxygen concentration.	More time spent at the target SaO_2 ($p < 0.025$), $SaO_2 < 90\%$ less frequent ($p < 0.01$) and less overall variations during the experimental period than during either control period.
CLAURE, 2001	Mechanically ventilated very low birthweight infants	Prospective clinical trial N=14 Closed-loop FiO_2 control ($cFiO_2$) to maintain SpO_2 within a target range was compared with continuous manual FiO_2 ($mFiO_2$) adjustments by a nurse.	$cFio_2$ is noninferior to a fully dedicated nurse in maintaining Spo_2 within the target range. Mean SpO_2 and FiO_2 levels were similar in both modes. Significant increase in the duration of normoxemia during cFio2 (75 +/- 13 vs 66 +/- 14%).

CLAURE, 2011	Mechanically ventilated preterm infants	Crossover study N=32 Automated versus manual adjustment of the fraction of inspired oxygen (FiO_2).	Time with SpO_2 in goal range increased significantly during the automated period compared to the manual period (40 +/- 14% versus 32 +/- 13%), less time spent hyperoxic in the automated period. Statistically significant increase in the time spent hypoxic in the automated period (32% ± 12% vs 23% ± 9%).
HALLENBERGER, 2014	Preterm infants receiving mechanical ventilation or nasal continuous positive airway pressure and supplemental oxygen	Multicenter, randomized controlled, crossover clinical trial N=34 Routine manual control of FIO_2 versus a closed-loop automatic control (CLAC).	Median percentage of time with SaO2 levels within target range was 61.4% (31.5-99.5) for routine manual control and 71.2% (44.0-95.4) for CLAC ($p<0.001$).
DIJKMAN, 2025	Extremely preterm infants who survived to NICU discharge and	Prospective cohort study; patients matched 1:1 with a control cohort who received routine manual FiO_2 control N=25 Comparison of FiO_2 control by the PRICO-automated FiO_2 controller versus routine manual care (RMC).	When requiring supplemental oxygen during the first 2 weeks of life, time within the SpO_2 target range significantly increased with FiO_2-c, while time in hyperoxia decreased.
DIJKMAN, 2023	Preterm infants on different modes of invasive and noninvasive respiratory support	Feasibility study N=32 Observation of infants receiving FiO2 control by the PRICO automated controller.	The time percentage within the SpO2 target range was increased with PRICO (74.4% [IQR 67.8-78.5]) compared to RMC1 (65.8% [IQR 51.1-77.8]; $p = 0.011$) and RMC2 (60.6% [IQR 56.2-66.6]; $p < 0.001$).
DIJKMAN, 2021	Preterm patients on high flow nasal cannula support receiving FiO2 > 0.25	Single-center randomized two-period crossover study N=27 Comparison of FiO2 control by the PRICO-automated FiO2 controller versus routine manual care (RMC).	The mean time within the target range increased with PRICO: 10.8% (95% CI 7.6 to 13.9). No difference in time spent in severe hyperoxia. There was a decrease in time below target range: 7.6% (95% CI 4.2 to 11.0), above target range: 3.1% (95% CI 2.9 to 6.2) and in severe hypoxia: 0.9% (95% CI 1.5 to 0.2). Mean FiO_2 was higher during PRICO: 0.019 (95% CI 0.006 to 0.030).
WILINSKA, 2024	Mechanically ventilated infants in neonatal intensive care	Multicenter randomized crossover study N=39 Evaluate the performance of the PRICO system for automated control of FiO_2.	During automated control, subjects spent more time in normoxemia (74%±22% vs 51%±22%, $p<0.001$ Patients spent less time in severe hyperoxemia (1% (0%-3.5%) vs 5% (1%-10%), $p < 0.001$).
SALVERDA, 2021	Infants of 24-29 weeks gestational age receiving respiratory support	Retrospective pre-post implementation cohort study N=588 (293 pre-implementation, 295 post-implementation) Comparison of routine care versus AOC.	Length of stay in NICU was not different, but duration of invasive ventilation was shorter in infants who received AOC (6.4 ± 10.1 vs 4.7 ± 8.3, $p = 0.029$).

Abbreviations: Fraction of inspired oxygen (FiO_2), arterial partial pressure of oxygen (PaO_2), respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), peripheral oxygen saturation (SpO_2), arterial oxygen saturation (SaO_2), closed-loop FiO_2 control ($cFiO_2$ or FiO_2-c), closed-loop automatic oxygen control (CLAC), chronic obstructive pulmonary disease (COPD), confidence interval (CI), interquartile range (IQR), routine manual control (RMC), Predictive Intelligent Control of Oxygenation (PRICO), automated oxygen control (AOC), neonatal intensive care unit (NICU)

Oxygen-related injury results from the combined effect of FiO_2 levels and exposure time, without a single threshold. Short exposure to very high FiO_2, such as during pre-oxygenation for intubation or brief surgeries, mainly causes reversible absorption atelectasis and is usually tolerated. Conversely, prolonged exposure to even moderate FiO_2 levels (0.40–0.60) can induce sustained production of reactive oxygen species, cytokine activation, and epithelial cell damage. Human studies show increased inflammatory markers within about 6 hours of high oxygen, decreased vital capacity after 24–48 hours at FiO_2 ≥0.75, and signs of diffuse pneumonitis after exposures longer than 48 hours.

Along with clinical measures like implementation of automated oxygen controllers, there are a number of potential molecular targets that have the potential to reduce tissue injury secondary to exposure to excess oxygen. Examples include connective tissue growth factor antibodies to improve alveolarization and vascularization[23], administration of mesenchymal stromal cell extracellular vesicles to improve thymic medullary architecture[68], and N-acetylcysteine (NAC) to mitigate hyperoxia-induced gut injury by reducing ROS production.[22] However, clinical trials evaluating their role in patient management are currently not available.

Conclusion

While oxygen therapy remains a cornerstone in the management of hypoxemia, excessive oxygen delivery poses underappreciated risks across patient populations. The pulmonary system is particularly vulnerable, as prolonged exposure to high FiO_2 and hyperoxemia initiates a cascade of oxidative, inflammatory, and structural injuries mediated by reactive oxygen species and altered cellular signaling. Despite decades of research, a definitive threshold for safe oxygen administration in humans remains elusive, as both cellular tolerance and systemic responses vary by context, duration, and disease state. The challenge lies in achieving adequate oxygenation without crossing into toxicity—a balance that can be difficult to maintain during dynamic clinical conditions. Recent advances, such as automated and closed-loop FiO_2 controllers, show promise in minimizing episodes of hyperoxia and hypoxia, thereby reducing preventable injury and improving ventilation outcomes. Parallel progress in molecular therapeutics—including antioxidants, targeted growth factor modulation, and stem cell–derived interventions—suggests a future in which oxygen toxicity may be mitigated at both the system and cellular level. Continued integration of physiologic monitoring, precision automation, and translational molecular research will be essential to redefine safe oxygen delivery and optimize outcomes for critically ill patients.

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