

The Impact of Hyperoxia in the Critically Ill Patient: A Review of the Literature

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Oxygen has long been considered a vital and potentially life-saving component of emergency care. Given this, there is widespread and liberal use of supplemental oxygen in hospitals across the United States and throughout the world. Recent research, however, delineates serious deleterious effects at the cellular level, inducing damage to the cardiovascular system, the central nervous system, the pulmonary system, and beyond. A scoping review was conducted to identify and synthesize available research data as it pertains to the clinical effects of hyperoxia in critically ill adult patients in acute care settings. We searched PubMed, MEDLINE, CINAHL, and Scopus databases. We also reviewed the reference lists of included publications. The selection of relevant articles was conducted by 2 researchers at 2 levels of screening. The review identified 30 studies, of which 5 were randomized controlled trials, 2 were prospective cohort studies, and 23 were retrospective cohort studies. A descriptive analysis of study results was performed. Current evidence suggests an association between hyperoxia and increased mortality after cardiac arrest, stroke, and traumatic brain injury, as well as in the setting of sepsis, although there is insufficient evidence to conclude concretely that hyperoxia effects clinical outcomes. As such, there exists a need for additional large-scale randomized controlled trials with well-defined parameters for the evaluation of clinical outcomes. Until the completion of such trials, titration of supplemental O₂ to normoxia is advised to avoid the negative effects of both hyperoxia and hypoxia in acutely ill adult patients. *Key words:* hyperoxia; hypoxia; critical care; emergency department; intensive care unit; acute coronary syndrome. [Respir Care 2020;65(8):1202–1210. © 2020 Daedalus Enterprises]

Introduction

Oxygen has long been identified as a vital and potentially life-saving component of acute care. Since its first application as treatment in the acute care setting in 1885,¹ supplemental O₂ has remained essential in the treatment of

hypoxia.² As a result, there has long been widespread and liberal use of supplemental O₂ in hospitals across the United States and throughout the world. Recent advances in technology and research, however, have identified several potential negative effects of excessive O₂, which is a physiological state better known as hyperoxia. This is

thought to be primarily due to oxygen's impact as an oxidizing agent. This feature of O₂ allows for serious deleterious effects at the cellular level, which can manifest as vasoconstriction, inflammation, and the formation of reactive oxygen species (ROS), and these effects induce damage in the cardiovascular system, the central nervous system, the pulmonary system, and beyond.³

Despite these concerns, guidelines for safe and effective use of supplemental O₂ are limited, and most health care professionals remain unaware of the negative effects of hyperoxia. Most decisions regarding the initiation of supplemental O₂ in critically ill patients occur in the emergency department, given its role as an entry point for hospital care; however, O₂ is often continued in the inpatient setting after admission from the emergency department. With this in mind, there is a clear need for clinical guidance on a possible threshold value or optimal range for arterial P_{aO₂}. To best facilitate improved management of hypoxia without iatrogenic effects, a greater comprehension of the optimum, nontoxic level of P_{aO₂} in critically ill adult patients must be further investigated. For this reason, we performed a literature review to assess the clinical effects of hyperoxia in critically ill adult subjects in acute care settings.

Search Strategy

For this narrative literature review, we searched the PubMed, MEDLINE, CINAHL, and Scopus databases to assess the literature on hyperoxia as it relates to patients with urgent or emergent medical conditions. The terms "hyperoxia," "oxygen inhalation therapy," and "emergency" were used. Search results were further limited to English language, human, adult, and publication date within the last 10 years. In total, 30 studies were included in the analysis. These studies included 5 randomized controlled trials (RCTs), 2 prospective cohort studies, and 23 retrospective cohort studies. Each of the selected articles was read in its entirety, and close attention was paid to the study design, sample size, definition of hyperoxia or flow of supplemental O₂, condition of the subjects included, and the location of the study.

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Hyperoxia in the Critically Ill Subject

Our literature search identified 30 articles assessing the relationship between hyperoxia and clinically relevant outcomes in critically ill adult subjects. Subsequent review of these studies revealed 5 broad categories with original research, including cardiovascular conditions, neurological conditions, respiratory failure, sepsis, and mixed intensive care conditions. Details pertaining to each individual study, including design, sample size, and definition of hyperoxia, as well as their main conclusions, are summarized in tables in this article.

Cardiovascular Conditions

The effects of hyperoxia in cardiovascular conditions, specifically in myocardial infarction and cardiac arrest, have been studied extensively. Not only does hyperoxia reduce cardiac output and stroke volume and increase systemic vascular resistance, it also causes a marked reduction in coronary blood flow and myocardial oxygen consumption.⁴ In addition to these pathophysiologic effects, hyperoxia increases the potential for reperfusion injury due to increased production of ROS.⁵ Beyond these effects, studies evaluating the association between hyperoxia and outcomes in cardiovascular conditions are summarized in Table 1.

In studies evaluating the association between hyperoxia and myocardial infarction, results are mixed. In subjects with uncomplicated ST-segment elevation myocardial infarction (STEMI) randomized to high-concentration O₂ (6 L/min via medium concentration mask) or titrated O₂ (to achieve oxygen saturation 93–96%), no evidence was found to support benefit or harm in terms of 30-d mortality and infarct size.⁶ Similarly, a larger study of subjects with suspected STEMI or NSTEMI randomized to supplemental O₂ or ambient air found no reduction in 1-y all-cause mortality.⁷ Conversely, a multicenter RCT found the use of 8 L/min of supplemental O₂ to be associated with both increased myocardial injury and infarct size at 6 months.⁸ However, this particular study was limited due to a lack of blinding of treatment allocation to paramedics, subjects, or in-hospital cardiology teams. Therefore, although the effects of hyperoxia in patients with recent myocardial infarction remains somewhat unclear, there is no denying the potential for serious deleterious side effects. Given this, there is a need for fully blinded and high-powered studies to further our understanding of the association between hyperoxia and myocardial infarction.

Similar to myocardial infarction, a significant amount of original research exists evaluating hyperoxia in the context of cardiac arrest.^{9–16} However, most of the existing studies are observational in design, and few are prospective in nature. P_{aO₂} > 300 mm Hg during out-of-hospital

Table 1. Association Between Hyperoxia and Clinically Relevant Outcomes for Cardiovascular Conditions

Reference	Study Design	Sample Size	Hyperoxia Definition or Rate of Supplemental Oxygen	Condition	Location	Conclusion
Ranchord et al ⁶	Randomized controlled trial	136	O ₂ at 6 L/min	Myocardial infarction	In-patient unit	No evidence of benefit or harm from high-concentration O ₂ compared with titrated O ₂ in initially uncomplicated STEMI.
Hofmann et al ⁷	Randomized controlled trial	6,629	O ₂ at 6 L/min	Myocardial infarction	Emergency department, critical care unit, catheter lab	Routine use of supplemental O ₂ in subjects with suspected myocardial infarction who did not have hypoxemia was not found to reduce 1-y all-cause mortality.
Stub et al ⁸	Randomized controlled trial	441	O ₂ at 8 L/min	Myocardial infarction	Hospital with 24-h PCI	Supplemental O ₂ therapy in patients with STEMI but without hypoxia may increase early myocardial injury and was associated with larger myocardial infarct size assessed at 6 months.
Vaahersalo et al ⁹	Prospective cohort	409	P _{aO₂} > 225 mm Hg	Cardiac arrest	ICU	Unable to identify any harm related to hyperoxia exposure.
Helmerhorst et al ¹⁰	Retrospective cohort	5,258	P _{aO₂} > 300 mm Hg	Cardiac arrest	ICU	Hyperoxia is not associated with greater in-hospital mortality.
Bellomo et al ¹¹	Retrospective cohort	12,108	P _{aO₂} ≥ 400 mm Hg	Cardiac arrest	ICU	Among subjects admitted to the ICU after cardiac arrest, hyperoxia did not have a robust or consistently reproducible association with mortality.
Spindelboeck et al ¹²	Retrospective cohort	1,015	P _{aO₂} > 300 mm Hg	Cardiac arrest	Prehospital	Significantly increased rate of hospital admission, but not neurologic outcome, associated with increasing P _{aO₂} .
Kilgannon et al ¹³	Retrospective cohort	6,326	P _{aO₂} ≥ 300 mm Hg	Cardiac arrest	ICU	Among subjects admitted to the ICU following resuscitation from cardiac arrest, arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia.
Elmer et al ¹⁴	Retrospective cohort	184	P _{aO₂} > 300 mm Hg as severe, P _{aO₂} 101–299 mm Hg as moderate or probable	Cardiac arrest	In-patient unit	Severe hyperoxia was independently associated with decreased survival to hospital discharge, whereas moderate or probable hyperoxia was not associated with decreased survival and was associated with improved organ function at 24 h.
Janz et al ¹⁵	Retrospective cohort	170	Continuous variable	Cardiac arrest	Critical care unit	Higher levels of maximum measured P _{aO₂} are associated with increased in-hospital mortality and poor neurological status on hospital discharge in subjects treated with mild therapeutic hypothermia after sudden cardiac arrest.
Kilgannon et al ¹⁶	Retrospective cohort	4,459	Continuous variable	Cardiac arrest	ICU	Dose-dependent association with supranormal O ₂ tension and in-hospital death.
Munshi et al ¹⁷	Retrospective cohort	1,952	P _{aO₂} > 101–300 mm Hg as moderate, P _{aO₂} > 300 mm Hg as severe	Extracorporeal life support	Unknown	Moderate hyperoxia was associated with increased mortality in subjects undergoing venovenous extracorporeal membrane oxygenation for respiratory failure and extracorporeal cardiopulmonary resuscitation.

STEMI = ST-segment elevation myocardial infarction
 PCI = percutaneous coronary intervention

Table 2. Association Between Hyperoxia and Clinically Relevant Outcomes for Neurological Conditions

Reference	Study Design	Sample Size	Hyperoxia Definition or Rate of Supplemental Oxygen	Condition	Location	Conclusion
Raj et al ²¹	Retrospective cohort	1,116	$P_{aO_2} > 100$ mm Hg	Traumatic brain injury	ICU	Hyperoxia in the first 24 h of ICU admission after moderate-to-severe traumatic brain injury is not predictive of 6-month mortality.
Davis et al ²²	Retrospective cohort	3,420	$P_{aO_2} > 487$ mm Hg	Traumatic brain injury	Level 1 or level 2 trauma centers	Both hypoxemia and extreme hyperoxia are associated with increased mortality and a decrease in good outcomes among subjects with traumatic brain injury.
Brenner et al ²³	Retrospective cohort	1,547	$P_{aO_2} > 200$ mm Hg	Traumatic brain injury	Level 1 trauma center	Hyperoxia within the first 24 h of hospitalization is associated with worse short-term functional outcomes and higher mortality after traumatic brain injury.
Rincon et al ²⁴	Retrospective cohort	1,212	$P_{aO_2} \geq 300$ mm Hg	Traumatic brain injury	ICU	In ventilated subjects admitted to the ICU, arterial hyperoxia was independently associated with higher in-hospital case fatality.
Rincon et al ²⁵	Retrospective cohort	2,849	$P_{aO_2} \geq 300$ mm Hg	Stroke	ICU	In ventilated subjects admitted to the ICU, arterial hyperoxia was independently associated with in-hospital death as compared with either normoxia or hypoxia.
Rincon et al ²⁶	Retrospective cohort	1,388	$P_{aO_2} \geq 300$ mm Hg	Intracerebral hemorrhage	ICU	In ventilated ICU subjects, failure to normalize hyperoxia was associated with higher case-fatality.
Fallenius et al ²⁷	Retrospective cohort	3,033	$P_{aO_2} > 150$ mm Hg	Intracerebral hemorrhage	ICU	No significant relationship between P_{aO_2} and long-term mortality.

cardiopulmonary resuscitation revealed a significant increase in hospital admission.¹² Furthermore, additional studies reported that cases of arterial hyperoxia with similar P_{aO_2} values were associated with increased in-hospital mortality.^{13,14} Historically, post-cardiac arrest patients are treated with mild therapeutic hypothermia because it has been reported to improve neurological outcomes and reduce mortality. For this reason, evaluation of hyperoxia in patients with concurrent mild therapeutic hypothermia is clinically relevant. A retrospective analysis of these subjects showed increased in-hospital mortality and worse neurological status on hospital discharge.¹⁵

Given the body of evidence suggesting an association between hyperoxia and increased risk of mortality in post-cardiac arrest patients, a retrospective analysis sought to determine whether the risk of adverse outcome is a dose-dependent association or a threshold effect at a specific supranormal P_{aO_2} value.¹⁶ Although there was no evidence to support a single threshold for harm as it relates to hyperoxia, there was a linear dose-dependent relationship in the association between abnormally elevated P_{aO_2} and relative risk of in-hospital mortality. This is an important clinical finding, but it has yet to be reproduced in a higher level of evidence study. More recently, moderate hyperoxia was

found to be associated with increased mortality in patients undergoing venovenous extracorporeal membrane oxygenation for respiratory failure and extracorporeal cardiopulmonary resuscitation.¹⁷

Neurologic Conditions

Similar to its effects on coronary blood flow, hyperoxia-induced vasoconstriction reduces cerebral perfusion, which may reduce intracranial pressure in head injury.¹⁸ However, it is well established that reduced cerebral oxygenation after brain injury is known to cause impaired mitochondrial function and reduced metabolic rate, which in turn increases the risk of secondary brain damage^{19,20} (Table 2).

Traumatic brain injury is perhaps the best-studied neurologic condition in terms of the delineation of the effects of hyperoxia. Of the studies included in this review that evaluated the association of hyperoxia in traumatic brain injury,²¹⁻²⁴ the majority were suggestive of worse outcome or greater risk of mortality. A retrospective review of subjects with traumatic brain injury at level 1 or level 2 trauma centers reported that both hypoxia and extreme hyperoxia, which was defined by investigators as $P_{aO_2} > 487$ mm Hg,

Table 3. Association Between Hyperoxia and Clinically Relevant Outcomes for Respiratory Failure

Reference	Study Design	Sample Size	Hyperoxia Definition or Rate of Supplemental Oxygen	Condition	Location	Conclusion
Wijesinghe et al ³³	Retrospective cohort	250	Continuous Variable	COPD exacerbation	Prehospital	In COPD exacerbation, high-flow oxygen in the ambulance and subsequent increases in P_{aO_2} were associated with greater risk of a poor outcome.
Cameron et al ³⁴	Retrospective cohort	254	$P_{aO_2} > 100$ mm Hg	COPD exacerbation	Emergency department	In subjects presenting to the emergency department with COPD exacerbation, serious adverse clinical outcomes were associated with both hypoxemia and hyperoxia.

were associated with increased mortality and a decrease in good outcomes, defined as discharge to home, rehabilitation, jail, or psychiatric facility, or leaving against medical advice.²² Similarly, a separate study of subjects with severe traumatic brain injury found that hyperoxia within the first 24 h of hospitalization was associated with worse short-term functional outcomes as measured by Glasgow Coma Scores on discharge.²³ As for ventilated traumatic brain injury subjects admitted to the ICU, arterial hyperoxia, defined as $P_{aO_2} > 300$ mm Hg, was reported to be independently associated with higher in-hospital case mortality.²⁴

As outlined in Table 2, similar associations have been established for those who have experienced stroke or cerebral hemorrhage.²⁵⁻²⁷ When defined as $P_{aO_2} > 300$ mm Hg, hyperoxia in ventilated subjects with recent stroke or cerebral hemorrhage has been found to be independently associated with in-hospital mortality and a higher case-fatality rate.^{25,26} However, when hyperoxia is defined as $P_{aO_2} > 150$ mm Hg and the evaluation period is extended beyond the subject's hospital stay, there was no significant relationship between hyperoxia and 6-month mortality.²⁷

Respiratory Failure

Management of acute hypoxemic respiratory failure frequently includes the use of O_2 therapy. While beneficial in the short-term, inspiration of pure O_2 is known to impair pulmonary gas exchange as a result of inhibition of hypoxic pulmonary vasoconstriction.³ Furthermore, alveolar epithelial cells are at high risk for hyperoxic cytotoxicity due to the high concentrations of direct O_2 exposure, which leads to ROS causing further disturbances in the pulmonary system.²⁸ This effect, known as oxygen toxicity, was first described in 1899 by Dr J Lorraine Smith²⁹ and has since been further reviewed.³⁰ In addition to this, high fractions of inspired O_2 are known to promote absorptive atelectasis by displacement of alveolar nitrogen and suppress mucociliary clearance.^{31,32} As is apparent, the local effects of high inspired O_2 therapy have been extensively studied,

whereas there is currently a paucity of data as it pertains to the effects of hyperoxia in respiratory failure.

Thus far, the effects of hyperoxia in the pulmonary system have been studied most closely in patients experiencing COPD exacerbations (Table 3). Retrospective analysis of prehospital hyperoxia secondary to high-flow oxygen in those with COPD exacerbations revealed an association with increasing risk of mortality, assisted ventilation, or respiratory failure per 10 mm Hg higher P_{aO_2} .³³ Similarly, retrospective analysis of arterial blood gases for emergency department patients with COPD exacerbations showed an association between both hyperoxia and hypoxemia with serious adverse outcomes, which were defined as a composite of hypercapnic respiratory failure, assisted ventilation, or in-patient mortality.³⁴

Sepsis

Conflicting data exist on the association between hyperoxia and outcome in those with sepsis. Theoretically, hyperoxia may seem beneficial for various reasons. First and foremost, increased systemic vascular resistance may contribute to greater hemodynamic stability and reduced vasopressor requirements. In addition to this, increased formation of ROS may contribute to greater antimicrobial host defense, given their bactericidal properties. Conversely, sepsis itself is associated with increased ROS formation, which is believed to contribute to the tissue damage and organ dysfunction seen with this condition.

At this point in time, results from studies evaluating hyperoxia in sepsis are inconclusive and mixed (Table 4).³⁵⁻³⁸ Although a small prospective study reported the incidence of hyperoxia in subjects with sepsis to be high, researchers were unable to establish an association between elevated P_{aO_2} and mortality.³⁵ Similarly, a retrospective analysis of ICU subjects with severe sepsis or septic shock revealed no difference in mortality as it relates to P_{aO_2} , although investigators were unable to exclude a clinically worse outcome.³⁶ More recently, the multicenter HYPERS2S RCT evaluated the effect of

Table 4. Association Between Hyperoxia and Clinically Relevant Outcomes for Sepsis

Reference	Study Design	Sample Size	Hyperoxia Definition or Rate of Supplemental Oxygen	Condition	Location	Conclusion
Stolmeijer et al ³⁵	Prospective cohort	83	P _{aO₂} > 101 mm Hg (converted from 13.5 kPa)	Sepsis	Emergency department	In all, 92.8% of subjects had P _{aO₂} at or above the threshold for hyperoxia, although sample size limited the ability to determine an association between mortality and hyperoxia in those with sepsis.
Dahl et al ³⁶	Retrospective cohort	1,770	P _{aO₂} > 120 mm Hg (converted from 16.0 kPa)	Sepsis	ICU	No effect on mortality, but P _{aO₂} < 60 mm Hg and F _{IO₂} > 60% increased mortality.
Asfar et al ³⁷	Randomized controlled trial	434	F _{IO₂} = 1.0	Sepsis	ICU	Setting F _{IO₂} to 1.0 to induce hyperoxia might increase mortality in subjects with septic shock.
Demiselle et al ³⁸	Retrospective cohort	397	F _{IO₂} = 1.0	Sepsis	ICU	Hyperoxia may be associated with a higher mortality rate in subjects with septic shock using the Sepsis-3 criteria, but not in subjects with hypotension alone.

increased F_{IO₂} and fluid resuscitation on mortality in mechanically ventilated adult subjects with septic shock.³⁷ Interestingly, this trial found a significant difference in the overall incidence of serious adverse events between the hyperoxia and normoxia groups. Data revealed a clinically relevant doubling in the hyperoxia group regarding the number of subjects with ICU-acquired weakness and atelectasis. Furthermore, in subjects with septic shock, setting F_{IO₂} to 1.0 to induce arterial hyperoxia was found to potentially increase the risk of mortality. Subsequent post hoc analysis of subjects in whom a plasma lactate value was available at study inclusion assessed the effects of hyperoxia and normoxia in septic subjects requiring vasopressor therapy.³⁸ Findings from this analysis suggested that hyperoxia treatment for 24 h in subjects with septic shock, as defined by the Sepsis-3 definition, may be associated with a higher mortality rate. However, it is possible that there are different effects of O₂ according to the underlying cellular and metabolic status of each patient. Though impressive, the findings from the HYPERS2S trial³⁷ are limited due to early termination due to safety concerns, which created imbalances between groups in terms of sample size.

Mixed ICU Conditions

Use of supplemental O₂ is frequent in the management of patients admitted to the ICU. Given this, it is important to understand the association between hyperoxia and ICU mortality regardless of the initial cause for admission. At this time, conflicting data exist on the association between hyperoxia and outcome in mixed ICU conditions (Table 5).³⁹⁻⁴³ Retrospective analysis of mechanically ventilated adult ICU subjects determined that 49.8% had hyperoxia within the first 24 h of admission but found no association

with mortality.³⁹ Alternatively, the same study found hypoxia to be associated with increased in-hospital mortality. Similar results were reported for ventilated ICU subjects with severe traumatic injuries whereby hyperoxia within the first 24 h of admission showed no risk of increased mortality or worsened neurological outcome.⁴⁰

With that said, there is some evidence of worse outcome in patients with mixed ICU conditions. The incidence of ventilator-associated pneumonia is associated with hyperoxia on admission and the number of days spent with elevated P_{aO₂}.⁴¹ In addition, hypoxia in the emergency department in normoxic ICU patients has been reported to be an independent predictor of in-hospital mortality for mechanically ventilated ICU patients.⁴² A separate study compared the effects of conservative oxygen supplementation (ie, P_{aO₂} 70–100 mm Hg) versus conventional oxygen supplementation (ie, P_{aO₂} 100–150 mm Hg).⁴³ Not only were mortality rates lower in the conservative group, where only 25 subjects died compared to 44 subjects in the conventional group, there was also lower incidence of new infections and shock. As discussed in a previous editorial written by Niall Ferguson,⁴⁴ the results from this trial are limited by both the small sample size and the unplanned early termination of the trial, which may have helped to exaggerate the effect size.

Discussion and Future Directions

The pathophysiologic effects of hyperoxia in intensive care, emergency care, and perioperative medicine, particularly vasoconstriction, inflammation, and oxidative stress, are well established and have been reviewed previously.³ While these deleterious effects are unambiguous, the effects of hyperoxia on clinical outcomes in critically ill adult patients is just now starting to unfold. Although it

Table 5. Association Between Hyperoxia and Clinically Relevant Outcomes for Mixed ICU Conditions

Reference	Study Design	Sample Size	Hyperoxia Definition or Rate of Supplemental Oxygen	Condition	Location	Conclusion
Eastwood et al ³⁹	Retrospective cohort	152,680	$P_{aO_2} > 120$ mm Hg	Unspecified	ICU	There was an association between hypoxia and increased in-hospital mortality, but not with hyperoxia in the first 24 h in ICU and mortality in ventilated subjects.
Russell et al ⁴⁰	Retrospective cohort	471	Unspecified	Severe traumatic injuries	ICU	In mechanically ventilated subjects with severe traumatic injuries, hyperoxia in the first 24 h of admission was not associated with increased death or worsened neurological outcomes in a setting without brain tissue oxygenation monitoring.
Six et al ⁴¹	Retrospective cohort	503	$P_{aO_2} > 120$ mm Hg	Unspecified	ICU	Hyperoxia was independently associated with ventilator-associated pneumonia.
Page et al ⁴²	Retrospective cohort	688	$P_{aO_2} > 120$ mm Hg	Unspecified	ICU	Exposure to hyperoxia in the emergency department was common and associated with increased mortality in mechanically ventilated subjects achieving normoxia after ICU admission.
Girardis et al ⁴³	Randomized controlled trial	434	P_{aO_2} 100–150 mm Hg	Unspecified	ICU	Among critically ill subjects with an ICU stay ≥ 72 h, a conservative protocol for oxygen therapy versus conventional therapy resulted in lower ICU mortality.

remains clear that supplemental O_2 is necessary for critically ill adult patients with hypoxia, there is preliminary evidence suggesting increased risk of mortality in the setting of hyperoxia. At least one observational study suggests a linear dose-dependent relationship between hyperoxia and relative risk of in-hospital mortality,²² although this has not yet been reproduced in a higher level of evidence trial. With that in mind, it remains possible the harmful effects of O_2 depend on the degree of hyperoxia and may be more pertinent within specific subsets of patients at specific moments of their hospital course.

Currently the majority of studies are observational studies with few RCTs evaluating the effects of hyperoxia on clinical outcomes. The data from these heterogeneous, observational studies have been largely inconsistent in terms of their definitions of hyperoxia, primary and secondary outcomes, and ultimately their findings. Furthermore, the majority of the existing studies focus on the evaluation of ICU patients. Although a seemingly large percentage of critically ill adult patients likely require admission to the ICU, resuscitation of these patients is not limited to ICUs. Therefore, to more completely capture the effects of hyperoxia during the care of critically ill adult patients, it is recommended that future trials expand beyond critical care to emergency medicine, trauma care, prehospital emergency care, and in-patient units. More recent studies have focused on the titration of supplemental O_2 in both the prehospital and emergency department settings, with evidence suggesting that it is feasible and that oxygenation parameters in the

emergency department are improved with automated titration of O_2 versus manual titration of oxygen.⁴⁵⁻⁴⁷ Although these results do not pertain to the effects of hyperoxia on clinical outcomes, they are encouraging in that their methodologies may be implemented to guide future research to better assess the effects of hyperoxia in critically ill adult patients in all acute care settings.

Therefore, although evidence of the deleterious effects of hyperoxia on clinical outcome is preliminary, there is a clear need to establish an optimum range of O_2 saturation. Determining this range of values will help minimize the competing risk of hyperoxia and hypoxia in critically ill adult patients, which will improve our ability to achieve the best possible outcomes. With that said, we acknowledge that the association between supranormal P_{aO_2} and poor clinical outcomes is more complex than a range of threshold values. First and foremost, future studies should better determine whether the risk of adverse outcome is a dose-dependent association or a threshold effect at a specific supranormal P_{aO_2} , expanding upon the work of Kilgannon et al.¹⁶ In addition, future studies, preferably large-scale RCTs, should help delineate the factors contributing to this complex relationship. For example, does the duration of hyperoxia increase the likelihood or magnitude of adverse effects? Furthermore, are specific disease processes or patient populations more sensitive to the deleterious effects of elevated P_{aO_2} ? As our understanding of this relationship improves, our ability to care for critically ill adult patients will do so as well. Subsequently, any effect of hyperoxia on

neurological sequelae, quality of life, and mortality will be minimized.

Given the lack of data from RCTs, there are many options for future studies in each of the various acute care settings. Presumably there are numerous ongoing trials, however, ICU-ROX by Young et al⁴⁸ is the most notable with results expected soon. The purpose of ICU-ROX is to compare a conservative approach of oxygen therapy to a standard care approach in a cohort of adults receiving mechanical ventilation in the ICU. The pilot phase of ICU-ROX confirmed the feasibility of this trial, which should encourage others to evaluate similar oxygenation strategies outside the ICU setting. Given that the emergency department serves as the initial point of care for undifferentiated critically ill patients, we believe the emergency department is an ideal location for future research evaluating the effects of targeted O₂ therapy.

Completion of such research should influence practice guidelines so as to improve care for critically ill adult patients. Until the completion of these studies and the implementation of new practice guidelines, conservative titration of supplemental O₂ to normoxia is recommended in critically ill adult patients to avoid the harmful effects of both hyperoxia and hypoxia. In addition, as physicians caring for this patient population, we should rethink the often knee-jerk decision to place critically ill patients on supplemental O₂ unless there is clear evidence of hypoxia.

Limitations

This review has several limitations. First and foremost, there is variability in the definition of hyperoxia across the literature. In terms of study design, the number of observational studies included in this review is far greater than the number of prospective RCTs. Each of the included observational studies has inherent limitations common to all observational studies. Furthermore, retrospective studies cannot evaluate the dose or duration of hyperoxia exposure when evaluating its association with clinical outcome. In addition, some of the trials included in this review had small numbers of participants, for which it may be difficult to draw conclusions for larger populations. Other limitations include the exclusion of non-English language papers. Together, these limitations suggest a need for additional large-scale, prospective RCTs to better determine the effects of hyperoxia in critically ill adult patients.

Summary

There is an increasingly large body of evidence suggestive of an association between hyperoxia and increased mortality in critically ill adult subjects particularly in those with recent cardiac arrest, stroke, traumatic brain injury, and sepsis. With that said, this evidence remains

incomplete, given the lack of RCTs. Therefore, there is a need for additional large-scale RCTs with well-defined parameters for the evaluation of the effects of hyperoxia on clinical outcomes in acute care settings. Until the completion of such trials, a more conservative approach to supplemental O₂ is best to avoid the negative effects of both hyperoxia and hypoxia in critically ill adult patients.

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