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HYPEROXIA AND OXYGEN THERAPY IN EMERGENCY CONDITIONS: DOES MORE OXYGEN ALWAYS MEAN BETTER OUTCOMES? A NARRATIVE REVIEW

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ABSTRACT

Oxygen therapy remains one of the most frequently administered interventions in emergency and critical care medicine. Traditionally, supplemental oxygen has been perceived as a harmless and universally beneficial treatment for patients experiencing acute illness, trauma, or cardiorespiratory compromise. However, growing evidence accumulated over the last two decades suggests that excessive oxygen administration may be associated with adverse physiological effects and worse clinical outcomes. Hyperoxia, defined as an abnormally elevated partial pressure of oxygen in arterial blood, has emerged as an important and potentially modifiable factor in the management of critically ill patients. Numerous observational studies, randomized controlled trials, and meta-analyses have demonstrated associations between hyperoxia and increased mortality, neurological injury, oxidative stress, vasoconstriction, and organ dysfunction.

The purpose of this review is to summarize current evidence regarding the pathophysiology of hyperoxia and its clinical implications in emergency medicine and critical care. Particular emphasis is placed on acute conditions frequently encountered in emergency departments and intensive care units, including cardiac arrest, acute coronary syndromes, stroke, traumatic brain injury, sepsis, and acute respiratory failure. The review also discusses current guideline recommendations and highlights areas requiring further investigation. Contemporary evidence suggests that oxygen should be regarded as a drug requiring individualized dosing, monitoring, and titration rather than a universally beneficial intervention. Avoidance of both hypoxemia and hyperoxemia appears crucial for optimizing patient outcomes.

KEYWORDS

Hyperoxia, Oxygen Therapy, Emergency Medicine, Critical Care, Oxidative Stress, Resuscitation, Oxygen Toxicity

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1. Introduction

Oxygen is indispensable for aerobic metabolism and cellular survival. Since its therapeutic introduction in the late nineteenth century, supplemental oxygen has become one of the most widely used treatments in modern medicine. In emergency departments, ambulances, operating rooms, and intensive care units (ICUs), oxygen administration is frequently initiated immediately upon patient contact, often before a definitive diagnosis is established. Historically, clinicians have adopted the principle that providing additional oxygen is inherently beneficial and carries minimal risk (Chu et al., 2018).

This assumption was largely based on the observation that tissue hypoxia contributes significantly to organ dysfunction and mortality. Consequently, oxygen supplementation became a standard component of treatment protocols for myocardial infarction, stroke, trauma, sepsis, respiratory failure, and cardiac arrest (O'Driscoll et al., 2017). However, increasing understanding of oxygen physiology has challenged the traditional view that higher oxygen concentrations invariably improve outcomes.

Over the last twenty years, numerous studies have demonstrated that supraphysiological oxygen exposure may produce harmful effects. Hyperoxia has been associated with increased production of reactive oxygen species (ROS), endothelial dysfunction, systemic vasoconstriction, inflammatory activation, and cellular injury (Helmerhorst et al., 2015). These mechanisms may contribute to worsening neurological outcomes following cardiac arrest, increased infarct size after myocardial ischemia, and higher mortality in critically ill patients (Girardis et al., 2016).

The concept that both insufficient and excessive oxygen delivery may be detrimental has led to the emergence of a "Goldilocks principle" in oxygen therapy, emphasizing the importance of maintaining oxygenation within an optimal therapeutic range (Beasley et al., 2015). Contemporary guidelines increasingly recommend titrated oxygen administration based on peripheral oxygen saturation (SpO_2) targets rather than routine use of high-flow oxygen in all patients.

This review examines the physiological basis of oxygen transport, the mechanisms of hyperoxic injury, and the evolving evidence supporting conservative oxygen therapy strategies in acute and critical care settings.

2. Physiological Basis of Oxygen Transport and Delivery

2.1 Oxygen Transport in Humans

Oxygen transport is a complex physiological process involving pulmonary gas exchange, circulatory delivery, and cellular utilization. Oxygen enters the bloodstream through diffusion across the alveolar-capillary membrane and is transported primarily bound to hemoglobin, with a smaller fraction dissolved in plasma (West, 2012).

The oxygen content of arterial blood (CaO_2) can be calculated using the following equation:

$CaO_2 = (1.34 \times Hb \times SaO_2) + (0.003 \times PaO_2)$

where:

- Hb = hemoglobin concentration,
- SaO_2 = arterial oxygen saturation,
- PaO_2 = arterial oxygen partial pressure.

Under normal physiological conditions, hemoglobin is nearly fully saturated when arterial oxygen tension exceeds approximately 80–100 mmHg. Beyond this threshold, further increases in inspired oxygen concentration produce only modest increases in total oxygen content because dissolved oxygen contributes minimally to oxygen transport (Lumb, 2020).

Consequently, raising PaO_2 from 100 mmHg to 300 mmHg significantly increases arterial oxygen tension but results in only a small increase in oxygen content. This physiological principle underlies concerns regarding routine administration of excessive oxygen concentrations.

2.2 Oxygen Delivery and Consumption

Oxygen delivery (DO_2) depends on both arterial oxygen content and cardiac output:

$DO_2 = \text{Cardiac Output} \times CaO_2$

Adequate tissue oxygenation requires a balance between oxygen delivery and oxygen consumption (VO_2). Under normal circumstances, tissues extract approximately 25% of delivered oxygen, leaving a substantial physiological reserve (Vincent & De Backer, 2013).

When oxygen delivery decreases significantly, compensatory mechanisms are activated, including:

- increased cardiac output,
- enhanced oxygen extraction,
- redistribution of blood flow to vital organs.

However, excessive oxygen administration does not necessarily improve oxygen delivery once hemoglobin saturation approaches 100%. Instead, supranormal oxygen levels may initiate adverse physiological responses.

3. Definition and Classification of Hyperoxia

Although no universal definition exists, hyperoxia generally refers to arterial oxygen levels exceeding physiological requirements.

Common definitions include:

- Mild hyperoxia: PaO_2 >100 mmHg
- Moderate hyperoxia: PaO_2 >200 mmHg
- Severe hyperoxia: PaO_2 >300 mmHg

Some investigators define hyperoxia using oxygen saturation targets above 98–99%, while others employ arterial blood gas measurements (Helmerhorst et al., 2015).

The incidence of hyperoxia in critical care settings is substantial. Studies indicate that 30–60% of mechanically ventilated ICU patients experience episodes of arterial hyperoxia during hospitalization (de Jonge et al., 2008). Because oxygen is often administered without strict titration, exposure to excessive oxygen concentrations remains common despite growing awareness of potential harms.

4. Pathophysiology of Hyperoxic Injury

4.1 Reactive Oxygen Species Generation

The principal mechanism underlying oxygen toxicity involves excessive generation of reactive oxygen species (ROS).

Physiological ROS production occurs continuously during mitochondrial oxidative phosphorylation. Under normal circumstances, endogenous antioxidant systems—including superoxide dismutase, catalase, and glutathione peroxidase—maintain redox balance (Auten & Davis, 2009).

Hyperoxia overwhelms these protective mechanisms by increasing formation of:

- superoxide anion (O_2^-),
- hydrogen peroxide (H_2O_2),
- hydroxyl radicals ($OH^•$),
- peroxynitrite ($ONOO^-$).

Accumulation of ROS results in oxidative stress, a state characterized by cellular damage exceeding antioxidant defense capacity.

Oxidative stress contributes to:

- lipid peroxidation,
- protein oxidation,
- DNA damage,
- mitochondrial dysfunction,
- apoptosis.

These processes have been implicated in neurological injury, myocardial dysfunction, pulmonary toxicity, and multiorgan failure (Mach et al., 2011).

4.2 Endothelial Dysfunction

The vascular endothelium plays a crucial role in regulating blood flow and tissue perfusion. Hyperoxia impairs endothelial function through multiple mechanisms.

Increased ROS production reduces nitric oxide bioavailability by promoting formation of peroxynitrite. Nitric oxide is a key vasodilator responsible for maintaining vascular homeostasis. Reduced nitric oxide levels promote vasoconstriction and impair microcirculatory blood flow (Farquhar et al., 2009).

Experimental studies have demonstrated that hyperoxia can reduce coronary blood flow by approximately 20–30% in healthy individuals despite elevated arterial oxygen content. Similar effects have been observed in cerebral and peripheral circulation.

Paradoxically, therefore, hyperoxia may reduce oxygen delivery to tissues despite increasing arterial oxygen tension.

4.3 Inflammatory Activation

Hyperoxia also influences immune and inflammatory pathways.

Elevated oxygen concentrations stimulate activation of:

- nuclear factor-kappa B (NF-κB),
- proinflammatory cytokines,
- neutrophil recruitment,
- endothelial adhesion molecules.

Persistent activation of these pathways contributes to tissue injury and may exacerbate systemic inflammatory responses observed in critical illness (Kallet & Matthay, 2013).

Animal studies suggest prolonged hyperoxia can induce diffuse inflammatory changes resembling acute lung injury. Similar mechanisms may contribute to ventilator-associated lung damage in critically ill patients receiving high inspired oxygen fractions.

4.4 Pulmonary Toxicity

The lungs represent the primary target organ for oxygen toxicity because they are directly exposed to elevated oxygen concentrations.

Pulmonary manifestations include:

- tracheobronchitis,
- alveolar epithelial injury,
- surfactant dysfunction,
- atelectasis,
- diffuse alveolar damage.

Extended exposure to FiO_2 levels above 0.60 significantly increases the risk of oxygen-induced lung injury (Kallet & Matthay, 2013).

Absorption atelectasis represents another clinically important consequence of hyperoxia. High oxygen concentrations replace alveolar nitrogen, facilitating alveolar collapse and worsening ventilation-perfusion mismatch.

5. Cerebral Effects of Hyperoxia

The brain is particularly vulnerable to alterations in oxygen homeostasis. Although adequate oxygenation is essential for neuronal survival, excessive oxygen exposure may have detrimental neurological consequences.

Hyperoxia induces cerebral vasoconstriction through nitric oxide depletion and direct vascular smooth muscle effects. Studies have demonstrated reductions in cerebral blood flow ranging from 10% to 30% during exposure to high oxygen concentrations (Farquhar et al., 2009).

This reduction may be especially harmful following ischemic insults such as:

- cardiac arrest,
- ischemic stroke,
- traumatic brain injury.

In these conditions, compromised microcirculation already limits oxygen delivery. Hyperoxia-induced vasoconstriction may therefore aggravate secondary brain injury despite elevated arterial oxygen levels.

Experimental evidence also suggests excessive oxygen promotes neuronal apoptosis through mitochondrial dysfunction and oxidative stress. Animal models of cerebral ischemia consistently demonstrate increased neuronal injury following prolonged hyperoxic exposure.

These observations have generated considerable interest in the role of targeted oxygen therapy during post-resuscitation care and neurocritical illness.

6. Hyperoxia Following Cardiac Arrest

6.1 Rationale for Oxygen Administration During Resuscitation

Cardiac arrest is characterized by a sudden cessation of effective circulation, resulting in global ischemia and severe tissue hypoxia. Restoration of oxygen delivery is therefore a primary objective of cardiopulmonary resuscitation (CPR) and post-resuscitation care. Historically, guidelines recommended administration of 100% oxygen during and immediately after resuscitation to maximize oxygen availability and minimize the risk of hypoxemia (Perkins et al., 2021).

However, the pathophysiology of post-cardiac arrest syndrome has revealed that reperfusion injury may contribute substantially to neurological damage and mortality. During ischemia, cellular antioxidant systems become depleted. Upon restoration of circulation, sudden exposure to high oxygen concentrations promotes excessive generation of reactive oxygen species, exacerbating neuronal injury through oxidative stress and mitochondrial dysfunction (Kilgannon et al., 2010).

6.2 Observational Evidence

One of the most influential studies examining post-resuscitation hyperoxia was conducted by Kilgannon et al. (2010). In a multicenter cohort involving more than 6,000 patients, arterial hyperoxia following return of spontaneous circulation (ROSC) was independently associated with increased in-hospital mortality compared with normoxia.

Subsequent observational studies supported these findings. Bellomo et al. (2011) demonstrated that both severe hypoxemia and severe hyperoxemia were associated with worse outcomes, suggesting a U-shaped relationship between arterial oxygen tension and survival. Similar results were reported by Roberts et al. (2018), who observed increased mortality among patients exposed to prolonged hyperoxia during the first 24 hours after resuscitation.

Several mechanisms may explain these observations:

1. Increased oxidative stress.
2. Cerebral vasoconstriction.
3. Mitochondrial injury.
4. Amplification of reperfusion damage.
5. Increased inflammatory activation.

Collectively, these effects may contribute to secondary neurological injury after successful resuscitation.

6.3 Randomized Controlled Trials

Although observational studies demonstrated strong associations, causality remained uncertain. More recent randomized trials have attempted to evaluate conservative oxygen strategies in post-cardiac arrest care.

The EXACT trial and related investigations compared lower oxygen targets with conventional oxygen therapy. While differences in mortality were often not statistically significant, these studies consistently demonstrated that conservative oxygen strategies were feasible and reduced exposure to extreme hyperoxia (Schjørring et al., 2021).

The BOX trial further examined blood pressure and oxygenation targets in comatose survivors of out-of-hospital cardiac arrest. Although no significant differences in neurological outcomes were observed between oxygen target groups, the study reinforced concerns regarding routine exposure to excessive oxygen tensions (Møller et al., 2022).

6.4 Current Recommendations

Contemporary resuscitation guidelines increasingly emphasize oxygen titration following ROSC. Once reliable oxygen saturation monitoring is available, inspired oxygen concentration should be reduced to maintain arterial oxygen saturation between approximately 94% and 98% while avoiding hypoxemia (Perkins et al., 2021).

The shift away from prolonged administration of 100% oxygen represents one of the most important changes in post-cardiac arrest care over the last decade.

7. Hyperoxia in Acute Coronary Syndromes

7.1 Historical Perspective

For decades, oxygen therapy was routinely administered to all patients presenting with suspected acute myocardial infarction (AMI), regardless of oxygen saturation status. This practice originated from the assumption that increasing arterial oxygen content would improve oxygen delivery to ischemic myocardium and reduce infarct size.

Despite widespread adoption, the physiological basis for routine oxygen administration in normoxemic patients remained surprisingly weak.

7.2 Mechanisms of Potential Harm

Hyperoxia may adversely affect myocardial ischemia through several pathways.

Coronary Vasoconstriction

High oxygen concentrations induce coronary vasoconstriction, reducing coronary blood flow despite increased arterial oxygen content (Farquhar et al., 2009).

Studies in healthy volunteers have demonstrated reductions in coronary blood flow of up to 30% during hyperoxic exposure. In patients with coronary artery disease, such reductions may further compromise perfusion of already ischemic myocardial tissue.

Increased Systemic Vascular Resistance

Hyperoxia increases systemic vascular resistance and left ventricular afterload. Consequently, myocardial oxygen demand may paradoxically increase despite efforts to enhance oxygen supply.

Oxidative Injury

Excessive oxygen exposure promotes free radical generation, potentially exacerbating ischemia-reperfusion injury following restoration of coronary blood flow.

7.3 Clinical Evidence

The AVOID trial represented a major challenge to traditional oxygen therapy practices in AMI. In this randomized study, normoxemic patients with ST-elevation myocardial infarction (STEMI) received either supplemental oxygen or no oxygen therapy. Unexpectedly, patients receiving oxygen demonstrated larger infarct sizes and higher rates of recurrent myocardial infarction (Stub et al., 2015).

Subsequently, the DETO2X-AMI trial enrolled more than 6,000 patients with suspected myocardial infarction and normal oxygen saturation. Investigators found no significant reduction in mortality or major cardiovascular events among patients receiving routine oxygen therapy compared with ambient air (Hofmann et al., 2017).

These findings substantially altered clinical practice.

7.4 Guideline Changes

Current cardiology guidelines no longer recommend routine oxygen administration in normoxemic patients with acute coronary syndromes. Supplemental oxygen is generally reserved for individuals with oxygen saturation below 90–92%, respiratory distress, or evidence of hypoxemia (Ibanez et al., 2018).

This change exemplifies the broader movement toward individualized oxygen therapy rather than universal administration.

8. Hyperoxia and Acute Ischemic Stroke

8.1 Pathophysiological Considerations

Acute ischemic stroke results from interruption of cerebral blood flow, producing a central infarct core surrounded by potentially salvageable ischemic penumbra.

Because oxygen delivery is impaired within affected tissue, supplemental oxygen was historically considered beneficial. However, the unique physiology of cerebral circulation complicates this assumption.

Hyperoxia-induced cerebral vasoconstriction may reduce perfusion within ischemic regions, potentially offsetting any benefit from increased arterial oxygen content (Singhal, 2007).

Furthermore, ischemic neurons are particularly susceptible to oxidative injury. Reperfusion accompanied by excessive oxygen exposure may accelerate neuronal death through reactive oxygen species formation.

8.2 Clinical Studies

Several studies have examined normobaric oxygen therapy in acute ischemic stroke.

Initial pilot investigations suggested possible improvements in imaging biomarkers and neurological recovery. However, larger randomized trials failed to demonstrate consistent clinical benefit.

The Stroke Oxygen Study randomized more than 8,000 patients to routine oxygen supplementation, nocturnal oxygen supplementation, or standard care. Investigators found no significant differences in disability, mortality, or functional outcomes at follow-up (Roffe et al., 2017).

Similarly, meta-analyses have concluded that routine oxygen administration in nonhypoxemic stroke patients provides little or no clinical advantage.

8.3 Current Practice

Current stroke guidelines recommend supplemental oxygen only when oxygen saturation falls below approximately 94%. Avoidance of both hypoxemia and excessive hyperoxia is emphasized (Powers et al., 2019).

9. Hyperoxia in Traumatic Brain Injury

9.1 Complex Relationship Between Oxygen and Brain Injury

Traumatic brain injury (TBI) presents a unique challenge because secondary brain injury frequently results from inadequate oxygen delivery.

Early studies suggested that hyperoxia might improve cerebral tissue oxygenation and reduce ischemic injury. Consequently, aggressive oxygen administration became common in neurocritical care.

However, subsequent investigations revealed conflicting results.

Potential Benefits

Potential advantages of hyperoxia include:

- increased diffusion of oxygen into injured tissue,
- improved cerebral tissue oxygen tension,
- support of mitochondrial metabolism,
- reduction of localized ischemia.

Potential Risks

Conversely, hyperoxia may:

- worsen oxidative stress,
- promote neuronal apoptosis,
- reduce cerebral blood flow through vasoconstriction,
- amplify inflammatory responses.

9.2 Clinical Evidence

Observational studies have produced inconsistent findings.

Some reports demonstrated improved cerebral oxygenation without corresponding improvements in clinical outcomes. Others identified associations between severe hyperoxia and increased mortality following severe TBI (Davis et al., 2009).

Meta-analyses suggest that while moderate increases in oxygen tension may improve cerebral oxygen measurements, robust evidence supporting routine hyperoxic therapy remains lacking.

As a result, most experts advocate individualized oxygen targets rather than prolonged exposure to extreme hyperoxia.

10. Hyperoxia in Sepsis and Septic Shock

10.1 Biological Rationale

Sepsis is characterized by dysregulated host responses to infection, systemic inflammation, endothelial dysfunction, and microcirculatory abnormalities.

Theoretical arguments supporting hyperoxia include:

- enhanced bacterial killing,
- improved tissue oxygenation,
- support of neutrophil oxidative burst mechanisms.

These considerations led some investigators to propose liberal oxygen administration in septic patients.

10.2 Experimental Evidence

Animal studies initially suggested that elevated oxygen concentrations could augment antimicrobial defenses. However, prolonged hyperoxia also intensified oxidative stress, endothelial injury, and inflammatory activation.

These observations raised concerns regarding translation into human clinical practice.

10.3 The HYPERS2S Trial

The Hyperoxia and Hypertonic Saline in Septic Shock (HYPERS2S) trial provided important evidence regarding oxygen therapy in sepsis.

Patients with septic shock were randomized to receive either high-concentration oxygen or standard oxygen therapy. The study was terminated prematurely because of increased serious adverse events and concerns regarding mortality in the hyperoxia group (Asfar et al., 2017).

The findings challenged assumptions that higher oxygen levels improve outcomes in septic shock.

10.4 Clinical Implications

Current evidence does not support routine induction of hyperoxia in septic patients. Instead, oxygen therapy should be carefully titrated to maintain adequate oxygenation while minimizing exposure to excessive oxygen concentrations.

11. Hyperoxia in Mechanically Ventilated ICU Patients

Hyperoxia is particularly common among mechanically ventilated patients because inspired oxygen concentrations can be adjusted rapidly and often remain elevated longer than necessary.

Large observational studies have repeatedly demonstrated associations between prolonged hyperoxia and increased mortality among ICU populations (de Jonge et al., 2008; Helmerhorst et al., 2015).

Potential mechanisms include:

- ventilator-associated lung injury,
- oxidative pulmonary damage,
- systemic vasoconstriction,
- impaired microcirculation,
- mitochondrial dysfunction.

These findings have motivated several large randomized controlled trials comparing conservative and liberal oxygen strategies, which will be discussed in the next section.

12. Conservative versus Liberal Oxygen Therapy: Evidence from Randomized Controlled Trials

Over the last decade, increasing concerns regarding oxygen toxicity have prompted numerous randomized controlled trials (RCTs) comparing conservative and liberal oxygen administration strategies. These studies have sought to determine whether limiting oxygen exposure improves outcomes among critically ill patients while maintaining adequate tissue oxygenation.

The concept underlying conservative oxygen therapy is straightforward: oxygen should be administered in sufficient quantities to prevent hypoxemia but not in excess of physiological requirements. This approach contrasts with traditional liberal strategies, which frequently expose patients to arterial oxygen tensions substantially above normal physiological levels.

Several landmark trials have significantly influenced contemporary oxygen therapy practices.

12.1 The Oxygen-ICU Trial

One of the first major randomized studies examining oxygen targets in critically ill patients was the Oxygen-ICU trial conducted by Girardis et al. (2016).

Study Design

The investigators enrolled mechanically ventilated ICU patients and randomized them to either:

- Conservative oxygen therapy (PaO_2 70–100 mmHg; SpO_2 94–98%)
- Conventional oxygen therapy (PaO_2 up to 150 mmHg; SpO_2 97–100%)

Findings

The trial reported:

- Lower ICU mortality in the conservative oxygen group.
- Reduced incidence of shock.
- Lower rates of bloodstream infection.
- Reduced organ dysfunction.

The mortality reduction observed in the conservative group generated considerable interest because it suggested that oxygen therapy itself might represent a modifiable risk factor in critical illness.

Limitations

Despite its influence, the study had important limitations:

- Single-center design.
- Early termination.
- Smaller sample size than originally planned.

Nevertheless, Oxygen-ICU provided the first randomized evidence suggesting that avoiding hyperoxia might improve survival.

12.2 The ICU-ROX Trial

The ICU-ROX trial represented one of the largest investigations of oxygen therapy in critically ill adults (Mackle et al., 2020).

Study Population

More than 1,000 mechanically ventilated ICU patients were randomized to:

- Conservative oxygen therapy.
- Usual oxygen therapy.

The conservative strategy involved reducing FiO_2 whenever possible and avoiding SpO_2 values above 97%.

Results

The primary endpoint was ventilator-free days at day 28.

Investigators found:

- No significant difference in ventilator-free days.
- No statistically significant difference in mortality.
- Reduced exposure to hyperoxia in the conservative group.

Interpretation

Although ICU-ROX did not demonstrate a clear mortality benefit, the study showed that conservative oxygen therapy is feasible and safe in a large ICU population.

Importantly, subgroup analyses suggested potential benefits among patients with hypoxic-ischemic encephalopathy following cardiac arrest.

12.3 HOT-ICU Trial

The Handling Oxygenation Targets in the ICU (HOT-ICU) trial evaluated oxygen targets among patients with acute hypoxemic respiratory failure (Schjørring et al., 2021).

Study Design

More than 2,900 ICU patients were randomized to:

- Lower oxygen target (PaO_2 approximately 60 mmHg).
- Higher oxygen target (PaO_2 approximately 90 mmHg).

Results

The study demonstrated:

- No significant difference in 90-day mortality.
- No difference in major adverse events.
- No difference in duration of organ support.

Clinical Significance

The HOT-ICU trial suggested that lower oxygen targets are safe and do not increase mortality despite substantially reducing oxygen exposure.

These findings reinforced the notion that liberal oxygen administration may not provide meaningful clinical benefit.

12.4 LOCO₂ Trial

The Liberal or Conservative Oxygen Therapy in Acute Respiratory Distress Syndrome (LOCO₂) trial focused specifically on patients with ARDS (Barrot et al., 2020).

Results

The study was terminated prematurely because of safety concerns.

Investigators observed:

- Increased incidence of mesenteric ischemia in the conservative group.
- No significant mortality benefit.
- Potential risks associated with excessively restrictive oxygen targets.

Implications

The LOCO₂ trial highlighted an important principle: avoiding hyperoxia should not result in undertreatment of hypoxemia.

Both extremes may be harmful.

The results further support the concept of an optimal oxygenation window rather than a universally low oxygen target.

13. Evidence from Systematic Reviews and Meta-Analyses

As the number of oxygen therapy trials increased, several meta-analyses sought to synthesize available evidence.

13.1 Chu et al. Meta-analysis

One of the most influential systematic reviews was conducted by Chu et al. (2018).

Study Characteristics

The analysis included:

- 25 randomized controlled trials.
- More than 16,000 acutely ill adults.
- Multiple clinical settings.

Main Findings

Liberal oxygen therapy was associated with:

- Increased in-hospital mortality.
- Increased 30-day mortality.
- Increased long-term mortality.

The authors concluded that oxygen therapy should be administered conservatively whenever clinically feasible.

This publication significantly influenced international guideline development.

13.2 IOTA Meta-analysis

The Improving Oxygen Therapy in Acute Illness (IOTA) review further reinforced concerns regarding hyperoxia.

The investigators observed that mortality risk increased progressively as oxygen saturation exceeded physiological targets.

Their findings suggested that oxygen administration should be tailored to individual patient needs rather than routinely maximizing arterial oxygenation.

13.3 Recent Evidence Syntheses

More recent reviews have generally reached similar conclusions:

1. Hyperoxia appears harmful in several acute conditions.
2. Conservative oxygen strategies are usually safe.
3. Evidence remains heterogeneous across disease categories.
4. Optimal oxygen targets likely differ between patient populations.

Overall, current evidence favors avoidance of unnecessary hyperoxia while maintaining adequate tissue oxygenation.

14. Current International Guidelines

The evolving evidence base has led to substantial changes in guideline recommendations.

14.1 European Resuscitation Council (ERC)

The European Resuscitation Council recommends:

- 100% oxygen during active resuscitation.
- Rapid oxygen titration after ROSC.
- Target oxygen saturation between 94% and 98%.

The guidelines emphasize avoiding prolonged hyperoxemia during post-resuscitation care (Perkins et al., 2021).

14.2 American Heart Association (AHA)

The American Heart Association similarly recommends:

- Initial high-concentration oxygen during resuscitation.
- Reduction of FiO_2 once oxygenation monitoring becomes available.
- Maintenance of oxygen saturation between 92% and 98%.

The AHA specifically warns against prolonged exposure to excessive oxygen concentrations.

14.3 European Society of Cardiology (ESC)

The ESC guidelines for acute coronary syndromes recommend oxygen therapy only when:

- SpO_2 <90%.
- Respiratory distress is present.
- Hypoxemia is documented.

Routine oxygen administration in normoxemic myocardial infarction patients is no longer recommended (Ibanez et al., 2018).

14.4 Stroke Guidelines

Current stroke guidelines recommend:

- Oxygen supplementation only when saturation falls below approximately 94%.
- Avoidance of routine oxygen therapy in normoxemic patients.

These recommendations are based largely on the Stroke Oxygen Study and subsequent evidence syntheses (Powers et al., 2019).

14.5 Intensive Care Guidelines

Critical care societies increasingly support oxygen titration protocols designed to avoid both hypoxemia and severe hyperoxia.

Common target ranges include:

- SpO_2 92–96%.
- PaO_2 approximately 60–100 mmHg.

These targets seek to balance physiological oxygen requirements against risks associated with excessive oxygen exposure.

15. Why Hyperoxia Continues to Occur in Clinical Practice

Despite mounting evidence, hyperoxia remains common worldwide.

Several factors contribute to this phenomenon.

15.1 Historical Clinical Culture

For generations, clinicians were taught that oxygen is inherently beneficial.

This deeply ingrained belief remains difficult to change despite emerging evidence.

15.2 Fear of Hypoxemia

Physicians often perceive hypoxemia as a more immediate threat than hyperoxia.

Consequently, oxygen is frequently administered liberally to avoid even brief episodes of desaturation.

15.3 Monitoring Limitations

Pulse oximetry has important limitations.

When oxygen saturation approaches 100%, clinicians cannot easily distinguish between:

- PaO_2 100 mmHg.
- PaO_2 300 mmHg.
- PaO_2 500 mmHg.

As a result, substantial hyperoxia may remain undetected unless arterial blood gas analysis is performed.

15.4 Emergency Department Environment

Emergency medicine often requires rapid decision-making under uncertainty.

In unstable patients, clinicians frequently prioritize immediate oxygen supplementation while delaying titration until further assessment becomes possible.

16. Remaining Controversies

Although substantial evidence supports avoidance of severe hyperoxia, several unresolved questions remain.

Optimal Targets

The precise oxygen saturation range associated with the best outcomes remains uncertain.

Disease-Specific Variability

Different conditions may require different oxygen targets.

For example:

- Cardiac arrest survivors.
- ARDS patients.
- Traumatic brain injury patients.
- Septic shock patients.

may each have unique physiological requirements.

Individualized Medicine

Future approaches may incorporate:

- Continuous tissue oxygen monitoring.
- Cerebral oxygenation assessment.
- Microcirculatory evaluation.
- Personalized oxygen titration algorithms.

Such strategies may ultimately replace fixed oxygen targets.

17. Discussion

The accumulated evidence reviewed in this article challenges the longstanding belief that supplemental oxygen is universally beneficial and essentially harmless. Although oxygen remains one of the most important life-saving interventions in acute and critical care medicine, contemporary data indicate that both insufficient and excessive oxygen administration may adversely affect patient outcomes.

The traditional paradigm of liberal oxygen therapy developed during an era when the physiological consequences of hyperoxia were poorly understood. Clinicians reasonably focused on preventing hypoxemia, a condition clearly associated with organ dysfunction and death. However, advances in critical care physiology have demonstrated that supraphysiological oxygen tensions can trigger complex biological processes involving oxidative stress, endothelial dysfunction, inflammation, and microcirculatory impairment.

Evidence supporting cautious oxygen administration is strongest in post-cardiac arrest care, acute myocardial infarction, and general critical care populations. In these settings, hyperoxia has repeatedly been associated with worse clinical outcomes. The findings are particularly compelling because they are biologically plausible and supported by mechanistic studies demonstrating oxygen-induced vasoconstriction and oxidative injury.

Importantly, however, the available literature does not support an overly restrictive approach to oxygen administration. Studies such as $LOCO_2$ suggest that aggressive reduction of oxygen targets may also be harmful. Consequently, the emerging consensus emphasizes avoidance of both hypoxemia and severe hyperoxia.

The concept of oxygen as a drug has become increasingly relevant. Like any pharmacological therapy, oxygen possesses indications, contraindications, therapeutic ranges, and potential adverse effects. Appropriate prescribing therefore requires careful monitoring, individualized titration, and ongoing reassessment.

18. Clinical Implications

Several practical conclusions can be drawn from current evidence.

First, oxygen should not be administered routinely to normoxemic patients experiencing acute coronary syndromes or ischemic stroke. Multiple randomized trials have failed to demonstrate meaningful benefit in these populations.

Second, oxygen administration following return of spontaneous circulation should be rapidly titrated to avoid prolonged hyperoxemia. While high-concentration oxygen remains appropriate during active resuscitation, continuation after ROSC may increase neurological injury.

Third, mechanically ventilated ICU patients should undergo regular reassessment of oxygen requirements. Excessive FiO_2 levels frequently persist long after adequate oxygenation has been achieved.

Fourth, pulse oximetry targets should generally remain within physiologically appropriate ranges, most commonly between 92% and 96%, unless disease-specific considerations justify alternative targets.

Finally, clinicians should recognize that oxygen therapy represents an active intervention requiring the same attention to dosing and monitoring as vasoactive medications, antibiotics, or sedatives.

19. Future Directions

Several important questions remain unanswered.

Future research should focus on:

1. Disease-specific oxygen targets.
2. Individualized oxygen therapy algorithms.
3. Continuous tissue oxygenation monitoring.
4. Cerebral oxygenation-guided therapy.
5. Hyperoxia exposure duration thresholds.
6. Long-term neurological outcomes.
7. Biomarkers of oxygen toxicity.
8. Precision medicine approaches in critical care.

Technological advances may facilitate personalized oxygen administration strategies based on real-time assessment of tissue oxygen delivery rather than reliance solely on arterial oxygen saturation.

Artificial intelligence and closed-loop oxygen delivery systems may further optimize oxygen therapy in emergency and intensive care settings.

20. Conclusions

Oxygen remains a cornerstone of emergency and critical care medicine. Nevertheless, growing evidence indicates that excessive oxygen administration may be associated with significant physiological and clinical harm.

Hyperoxia contributes to oxidative stress, endothelial dysfunction, vasoconstriction, inflammatory activation, and organ injury. Randomized trials and meta-analyses increasingly support conservative oxygen therapy strategies aimed at avoiding unnecessary hyperoxemia while maintaining adequate tissue oxygenation.

Current evidence suggests that oxygen should no longer be viewed as a universally benign intervention. Instead, it should be considered a therapeutic agent requiring individualized prescription, careful titration, and continuous monitoring.

The optimal approach to oxygen therapy is not maximal oxygenation but rather achievement of physiological oxygen targets that balance the risks of hypoxemia against the potential harms of hyperoxia. Future research will further refine these targets and contribute to increasingly personalized oxygen management strategies in emergency and critical care medicine.

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