CONCISE CLINICAL REVIEW

CME

Oxygen Toxicity in Critically Ill Adults

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Abstract

Oxygen supplementation is one of the most common interventions in critically ill patients. Despite over a century of data suggesting both beneficial and detrimental effects of supplemental oxygen, optimal arterial oxygenation targets in adult patients remain unclear. Laboratory animal studies have consistently showed that exposure to a high $F_{I_{O_2}}$ causes respiratory failure and early death. Human autopsy studies from the 1960s purported to provide histologic evidence of pulmonary oxygen toxicity in the form of diffuse alveolar damage. However, concomitant ventilator-induced lung injury and/or other causes of acute lung injury may explain these findings. Although some observational studies in general populations of critically adults showed higher mortality in association with higher oxygen exposures, this finding has not been consistent. For some specific populations, such as those with cardiac arrest, studies have suggested harm from targeting supraphysiologic Pa_{O_2} levels. More recently, randomized clinical trials of arterial oxygenation targets in narrower physiologic ranges were conducted in critically ill adult patients. Although two smaller trials came to opposite conclusions, the two largest of these trials showed no differences in clinical outcomes in study groups that received conservative versus liberal oxygen targets, suggesting that either strategy is reasonable. It is possible that some strategies are of benefit in some subpopulations, and this remains an important ongoing area of research. Because of the ubiquity of oxygen supplementation in critically ill adults, even small treatment effects could have a large impact on a global scale.

Keywords: oxygen inhalational therapy; ICUs; hyperoxia

Since the discovery of oxygen in the 18th century, its life-giving properties have been known to coexist with the potential to damage and destroy (1). Although essential for cellular respiration, excess oxygen can lead to the production of reactive oxygen species (ROS), causing oxidative damage to cellular structures and activating cell-death pathways (2). Although there have been concerns about potential oxygen toxicity since its introduction into clinical medicine in the 1920s (3), optimal dosing of oxygen in critically ill patients remains unclear. Any effective strategy would need to balance the deleterious effects of hypoxemia with the potential consequences of direct pulmonary toxicity from high concentrations of inspired oxygen and systemic toxicity from high concentrations of oxygen in the blood (hyperoxemia) and tissues (hyperoxia). Given the prevalence of oxygen therapy in ICUs, an oxygen dosing strategy that optimized patient outcomes could be beneficial on a large scale. In this review, we outline the experimental and observational evidence for oxygen toxicity in critically ill patients. We then review the emerging data from clinical trials in critically ill patients with respiratory failure and discuss future research priorities.

Animal Models

Numerous studies in laboratory animals demonstrated that exposure to an $F_{I_{O_2}}$ greater than 0.7 over 3–6 days can cause death from progressive respiratory failure (4, 5). Histopathologic examination of these animals revealed diffuse alveolar damage comparable to acute respiratory distress syndrome (ARDS) (6). The species and age of the laboratory animals influenced susceptibility. For example, some studies showed that lower-order primates succumb to oxygen toxicity later in the course of high $F_{I_{O_2}}$ exposure than do rabbits or rodents (7–9). This apparent increased oxygen

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tolerance in primates is of unclear significance regarding oxygen's potential toxicity to humans. Although these studies suggest that cumulative exposure to high levels of $F_{I_{O_2}}$ is an important determinant of toxicity, other preclinical studies demonstrated the occurrence of biological changes with exposure to $F_{I_{O_2}}$ levels of <0.6 and at durations of ≤ 3 hours (10, 11).

Preclinical Studies in Humans

In one of the earliest systematic studies of oxygen tolerance in humans, young healthy volunteers breathed different concentrations of oxygen for up to 24 hours (12). Between Hours 12 and 16, most subjects receiving 100% oxygen developed cough, substernal chest discomfort, and a decrease in VC. These findings were also frequent in subjects breathing 75% oxygen but not in those breathing 50% oxygen. Subsequent studies of high oxygen exposure in humans demonstrated similar results (13–16). Substernal discomfort in this setting may be from local effects of absorptive atelectasis induced by nitrogen washout rather than from tissue damage due to oxygen toxicity. Atelectasis as a prominent mechanism is supported by a study in which resolution of substernal discomfort occurred with scheduled coughs and sighs (14). In another study, subjects breathed a mixture of 50% oxygen and 50% nitrogen at 2 atmospheres of pressure for 3 hours. In this design, high alveolar oxygen concentrations were maintained without nitrogen washout, and subjects did not experience substernal discomfort (14). High-$F_{I_{O_2}}$ breathing in both healthy and critically ill adults also affects gas exchange and can lead to increased intrapulmonary shunt and $\dot{V}/\dot{Q}$ mismatch (17, 18). This shunt may be reversed by the application of positive end-expiratory pressure (PEEP), again supporting atelectasis as the prominent mechanism (19). Other studies in healthy humans suggested direct pulmonary toxic effects. Bronchoscopic examination of research subjects exposed to a high $F_{I_{O_2}}$ showed erythematous airways, histologic evidence of tracheal inflammation (15, 20), and suppressed mucociliary clearance, a marker of tracheal epithelial dysfunction (20, 21). At the level of the alveolus, bronchoalveolar fluid from subjects breathing 50–100% oxygen for 17–45 hours contained increased concentrations of albumin and profibrotic mediators, suggesting early alveolar injury and increased vascular and epithelial permeability (15, 22). Although these studies suggest both local physiologic and direct tissue toxicity effects, most were conducted in healthy volunteers. Whether or not a high amount of inspired oxygen causes the same effects in critically patients and how these affect clinical outcomes is uncertain.

Context for Human Clinical Studies of Oxygen Toxicity

Autopsy studies in patients who had died of critical illness in the 1960s and 1970s provided the first human histopathologic evidence of lung injury potentially attributable to oxygen toxicity (23–26). Lung tissue from 70 patients who died after prolonged mechanical ventilation (MV) was compared with lung tissue from control patients who died but had not received MV (23). In the MV group, lung histopathologic analysis showed early exudative and late proliferative stages of what would later be recognized as diffuse alveolar damage (27). These findings were most frequent in patients with >10 days of MV with an $F_{I_{O_2}} \geq 0.9$. In another autopsy study, diffuse histopathologic lung injury was only found in those exposed to an $F_{I_{O_2}} \geq 40\%$ (26). However, these studies should be interpreted with caution. The practices of MV during this period used a larger $\dot{V}_T$ and lower PEEP than are used in current MV strategies. It is not clear whether the demonstrated lung injury was due to oxygen toxicity, ventilator-induced lung injury, or other causes of ARDS.

Several aspects of critical illness may influence susceptibility to oxygen toxicity. During critical illness, concomitant lung injury, systemic inflammation, increased metabolism, and preexisting tissue hypoxia may potentiate or modify the risks of oxygen toxicity (5). In animal experiments, injured lungs were more vulnerable to high-$F_{I_{O_2}}$ lung injury, although the timing of oxygen delivery in relation to initial injury affected this vulnerability (11, 28–32). In addition, hyperoxia may act synergistically with ventilator-induced lung injury, as shown in multiple animal models (33–35). Recent work also demonstrates that in both a mouse model and a cohort of critically ill humans, exposure to a high $F_{I_{O_2}}$ was associated with alterations in the lung microbiota (the community of microorganisms residing in the lung) (36). This change precedes the development of lung injury and leads to selection of oxygen-tolerant microbes such as *Staphylococcus aureus*. In this group of studies, a germ-free mouse model or preceding antibiotic treatment eliminated/prevented altered lung microbiota and attenuated subsequent development of lung injury. This suggests a causal mechanism of oxygen-induced injury that may be particularly relevant to infection-prone critically ill patients.

Damage from excessive oxygen can arise from both direct pulmonary toxicity from a high $F_{I_{O_2}}$ and from systemic effects of high Pa_{O_2} in blood and tissues (5, 37). Each pathway has shared and distinct mechanisms and may pose risks to different patient populations. Direct pulmonary toxicity from a high $F_{I_{O_2}}$ may occur from the elaboration of ROS. This can cause oxidative cellular damage and propagate a further inflammatory response (2). Systemic oxygen toxicity from tissue exposure to high Pa_{O_2} also involves ROS but can also lead to hyperoxemic vasoconstriction starting at Pa_{O_2} levels at or above 150 mm Hg (37). This vasoconstrictive effect differs across tissue beds and is prominent in brain, retinal, and cardiac tissue. Because of this, arterial oxygen content can increase while oxygen delivery decreases (37). These effects likely have differential impacts across populations of critically ill patients and need to be considered when developing oxygen-targeting schemes (Figure 1). For example, in a patient with severe underlying lung injury and impaired gas exchange, exposure to a high $F_{I_{O_2}}$ could increase the risk of pulmonary toxicity without increasing the risk of systemic toxicity, given an inability to obtain high Pa_{O_2}. On the other hand, patients without impaired gas exchange may have supraphysiologic Pa_{O_2} despite having an only modestly elevated $F_{I_{O_2}}$. In such patients, particularly in those with cardiac or brain ischemia, there may be an increased risk of reperfusion injury or decreased oxygen delivery from vasoconstriction in vulnerable tissue beds.

On the other hand, there also may be beneficial effects of hyperoxemia (38). Although dissolved oxygen contributes little to arterial oxygen content when the oxygen-carrying capacity is normal, even small increases in oxygen content may be helpful when there is an ongoing supply–demand mismatch. In some of these conditions, such

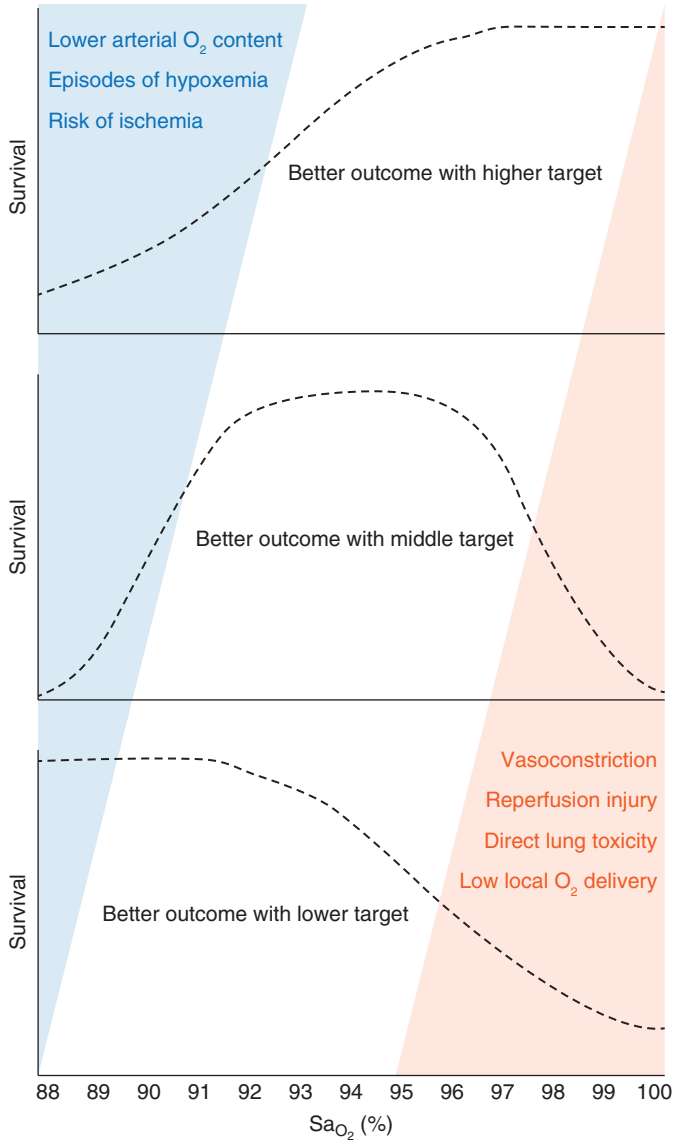

Figure 1. The risks of hypoxemia and hyperoxemia and the impact on higher versus lower arterial oxygenation targets for critically ill adults. The Sa_{O_2} values (*x*-axis) at which the potential detrimental effects of hypoxemia (blue triangle) or hyperoxemia (orange triangle) occur remain uncertain—and may differ for patients with different acute illnesses and comorbidities. If detrimental effects of hyperoxemia occur only at very high Pa_{O_2} values and detrimental effects from hypoxemia occur even with modestly low oxygen saturation as measured by pulse oximetry (Sp_{O_2})/Pa_{O_2} values, then using a higher Sp_{O_2} target might improve outcomes (dashed line in upper panel). Conversely, if even modestly supraphysiological Pa_{O_2} values incur the detrimental effects of hyperoxemia and only severely low Sa_{O_2}/Pa_{O_2} values incur the detrimental effects of hypoxemia, then using a lower Sp_{O_2} target might improve outcomes (dashed line in lower panel). Physiologically, patients with impaired oxygen delivery (e.g., anemia) or increased oxygen consumption (e.g., sepsis) might be hypothesized to experience better outcomes with a higher Sp_{O_2} target (upper panel), whereas patients adapted to chronic hypoxemia (e.g., chronic obstructive pulmonary disease) or certain types of brain injury (e.g., after cardiac arrest) might be hypothesized to experience better outcomes with a lower Sp_{O_2} target (lower panel).

as critical anemia or hemorrhagic shock, animal models have suggested that hyperoxemia may be beneficial (39). In addition, the surge in ROS that occurs with hyperoxemia has been proposed to be potentially beneficial for helping the immune system fight off infection (40, 41). These tradeoffs between the potential harms and benefits of hyperoxemia help to frame clinical studies of hyperoxia and hyperoxemia in critically ill patients.

Observational Studies in Critically Ill Adults

A number of observational studies have examined the associations between hyperoxemia and/or hyperoxia and clinical outcomes in populations of critically ill adults (42–55). Although there have been important studies involving high oxygen exposure in specific populations, such as in those with stroke, traumatic brain injury, perioperative settings, and trauma, we will focus on studies examining general populations of critically ill patients more commonly encountered in medical ICUs. Comparing these studies is complicated by varying definitions and durations of oxygen exposure (Table 1). However, a consistent finding is a U-shaped relationship between Pa_{O_2} and mortality in unadjusted analyses: that is, higher mortality in both hypoxemic and hyperoxemic patients (42, 43, 45, 47, 52, 53, 55). However, when the effect of exposure to the FI_{O_2} is carefully accounted for, studies have yielded conflicting results regarding the high Pa_{O_2}–mortality association (42, 43). Moreover, this biphasic relationship generally occurs in unadjusted analyses but is not always demonstrated in adjusted models, suggesting residual or unmeasured confounding and casting doubt on oxygen toxicity as a causal effect (43, 48, 51). In cohorts of patients who have suffered cardiac arrest, both retrospective (56, 57) and recent high-quality prospective observational data (58) showed increased mortality and worse neurologic outcomes in patients exposed to a Pa_{O_2} >300 mm Hg early in the course after cardiac arrest. Although there is inconsistency in these data, they raise concern for targeting supraphysiologic Pa_{O_2} levels and support a narrowing of oxygen targets to physiologic ranges.

Several studies have examined the effects of "excessive oxygen exposure," defined as the administration of an FI_{O_2} greater than required to maintain normal arterial oxygenation (42, 45, 46). In a small, single-center study, excessive oxygen exposure was defined as an FI_{O_2} >0.5 with an

Table 1. Observational Studies of Oxygenation in Critically Ill Adult Patients

Study	Study Population* (*n*)	Oxygen Exposure Metric	Association of Hyperoxia and Mortality in Adjusted Models?
de Jonge *et al.* (2008) (42)	Receiving IMV (36,307)	Pa_{O_2} and $F_{I_{O_2}}$ in first 24 h†	Yes
Eastwood *et al.* (2012) (43)	Receiving IMV (152,680)	Pa_{O_2} in first 24 h†	No
Rachmale *et al.* (2012) (44)	Patients with ALI receiving IMV for ⩾48 h (210)	Excessive $F_{I_{O_2}}$ ($F_{I_{O_2}}$ >0.5 with Sp_{O_2} >92%)	No
Helmerhorst *et al.* (2017) (45)	Patients with ⩾1 ABG (14,441)	Various‡ (i.e., mean/median Pa_{O_2} from ICU stay)	Yes
Kraft *et al.* (2018) (48)	IMV for ⩾7 consecutive d (20,889)	Time-weighted Pa_{O_2} over 7 d	No
Aggarwal *et al.* (2018) (46)	ARDS Network trials (all received IMV) (2,994)	Excessive $F_{I_{O_2}}$ ($F_{I_{O_2}}$ >0.5 with Pa_{O_2} >80 mm Hg)	Yes
Ramanan and Fisher (2018) (47)	Receiving IMV (219,732)	Pa_{O_2} in first 24 h§; analysis stratified by Hb	No
Ruggiu *et al.* (2018) (49)	ICU patients (130)	Any Pa_{O_2} >100 mm Hg during ICU admission	Yes
Palmer *et al.* (2019) (50)	ICU stay >24 h (45,188)	Time-weighted AUC for Pa_{O_2} >100 mm Hg	Yes
Harvey *et al.* (2020) (54)	Receiving IMV with ⩾3 ABGs (7,452)	Time-weighted Ca_{O_2} over ICU admission	Yes
Madotto *et al.* (2020) (51)	ARDS within 2 d of ICU admission (2,005)	Pa_{O_2} >100 mm Hg on ICU Day 1	No
Schjørring *et al.* (2020) (52)	Receiving IMV (4,998)	Time-weighted AUC Pa_{O_2} >13.7 kPa (103 mm Hg)	Yes
van den Boom *et al.* (2020) (53)	All ICU admissions (124,984/ 46,476)‖	Median Sp_{O_2}	Yes
Zhou *et al.* (2020) (55)	IMV in first 24 h of ICU (25,669)	Percentage of time spent at Sp_{O_2} of 100%	Yes

Definition of abbreviations: A–a = alveolar–arterial; ABG = arterial blood gas; ALI = acute lung injury; APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; AUC = area under the curve; Ca_{O_2} = arterial oxygen concentration; IMV = invasive mechanical ventilation; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.
*All study samples include ICU patients only.
†The Pa_{O_2} value was taken from blood gas with worst $Pa_{O_2}/F_{I_{O_2}}$ ratio in Reference 42 or from highest A–a gradient in Reference 43.
‡The purpose of the study was to evaluate multiple metrics; the mean/median Pa_{O_2} across the ICU stay had the strongest association with mortality.
§Taken from the Pa_{O_2} value associated with highest APACHE score.
‖Sample sizes from replicate analyses of two retrospective cohorts.

oxygen saturation as measured by pulse oximetry (Sp_{O_2}) >92% (44). A greater duration of exposure in the first 48 hours of ICU admission was associated with subsequent worsening of arterial oxygenation and longer durations of ICU admission and MV (44). Using a similar approach, a *post hoc* analysis of ARDS Network trial participants in the first 5 days of ICU admission showed an association of increased mortality with increasing days of excessive oxygen delivery, defined as Pa_{O_2} >80 mm Hg at an $F_{I_{O_2}}$ >0.5 (46). Although these studies suggest that cumulative measures of excessive oxygen exposure influence mortality, a similar analysis of the LUNG SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) observational study did not find an association between excessive oxygen exposure on ICU Day 1 and mortality in either adjusted models or a propensity score analysis (51).

Other investigators have used different methods to account for cumulative oxygen exposure. In a large observational study of critically ill patients, a Pa_{O_2} >100 mm Hg was considered a surrogate for excessive oxygen exposure (50). The "hyperoxemia dose" was modeled by using a time-weighted area under the curve measure of Pa_{O_2} >100 mm Hg, with higher values indicating a higher dose exposure. The occurrence of hyperoxemia examined over several different exposure windows was significantly associated with ICU mortality, but the hyperoxemia dose was not. To explain these results, it is possible that the occurrence of a high $F_{I_{O_2}}$ or high Pa_{O_2} during an ICU admission is a marker of increased mortality risk but is not a causal factor. For example, a transfer of a patient to an invasive procedure may occur on a 100% $F_{I_{O_2}}$. In addition, some clinicians may attempt to increase oxygen delivery in the sickest patients, and high Pa_{O_2} could hence potentially be a marker of illness severity. Finally, a higher than necessary $F_{I_{O_2}}$ or high Pa_{O_2} levels might show a lack of attention to $F_{I_{O_2}}$ titration by an ICU team and could indicate other differences in ICU care.

Some studies have suggested a dose–response relationship between cumulative measures of oxygen exposure and mortality (52, 53). In one study, a

dose–response relationship between a Pa_{O_2} area under the curve measure and mortality was shown and persisted regardless of whether the FI_{O_2} was ⩾0.4 or ⩽0.4 (52). If the results of this study are valid, reducing oxygen exposure even at a relatively lower FI_{O_2} could be beneficial. Another study in ICU patients examined the association of various Sp_{O_2} ranges throughout an ICU stay and mortality (53). A median Sp_{O_2} of 96% was associated with the lowest ICU mortality. Patients with more than 80% of their ICU time with Sp_{O_2} levels of 94–98% had lower mortality than those with less than 40% of their time in this range. Furthermore, those with more than 80% versus less than 40% of time with an Sp_{O_2} greater than 98% had increased odds of mortality, suggesting a possible contribution from hyperoxia. Given concern for the time-dependency of oxygen exposure, the investigators conducted sensitivity analyses limited to the first 24, 48, and 72 hours of oxygen therapy and found similar results.

A concern that is raised when targeting lower Sp_{O_2} and Pa_{O_2} targets is the occurrence of detected or undetected episodes of hypoxia. Although some immediate effects of hypoxia may be clinically apparent at the bedside, subtle long-term deficits related to hypoxia exposure may not occur until later. In one of the first studies to describe long-term cognitive outcomes in ARDS survivors, the amount of time spent with hypoxia was significantly correlated with worse neurocognitive performance at 1 year (59). In another study examining cognitive outcomes, each 10–mm Hg decrease in Pa_{O_2} was associated with an ∼50% increased odds of cognitive impairment at 1 year (60). Whether worse long-term cognitive function is attributable to hypoxia itself or whether hypoxia is associated with other factors that impair cognition remains unclear. Ongoing randomized trials of oxygen targets are collecting outcome data on long-term cognitive function to inform this issue.

Randomized Trials of Arterial Oxygen Targets for ICU Patients

Recent randomized controlled trials (RCTs) have begun to provide important data to inform our understanding of arterial oxygenation targets in general populations of critically ill patients (Table 2) (61–65). In the single-center OX-ICU (Oxygen–ICU trial), patients anticipated to need at least 72 hours of ICU care were randomized to conservative versus usual-care oxygenation targets. This population included, but was not exclusive to, patients receiving invasive MV (291/434 [67%]) (62). In the conservative group, Pa_{O_2} and Sp_{O_2} targets were 70–100 mm Hg and 94–98%. In the usual-care group, Pa_{O_2} could range up to 150 mm Hg, and the Sp_{O_2} goal was 97–100%. Patients with acute exacerbations of chronic obstructive pulmonary disease and moderate-to-severe ARDS were excluded. The conservative and usual-care groups had median Pa_{O_2} values of 87 mm Hg and 102 mm Hg and mean FI_{O_2} values of 0.36 and 0.39, respectively. In the conservative oxygen arm, there was an 8.6% absolute risk reduction in ICU mortality (95% confidence interval [CI], 1.7–15.0%). This trial was stopped early for slow recruitment.

In the ICU-ROX (ICU Randomized Trial Comparing Two Approaches to Oxygen Therapy) trial, 1,000 invasively mechanically ventilated patients were randomized to conservative versus usual-care oxygenation strategies titrated to Sp_{O_2} (64). In the conservative oxygen study group, the Sp_{O_2} target range was 91–96%, and FI_{O_2} was adjusted to the lowest level that achieved this range (including a FI_{O_2} of 0.21). In the usual-care arm, an Sp_{O_2} ⩾91% was also targeted, but there was no Sp_{O_2} upper limit, and in contrast to the conservative group, lowering the FI_{O_2} to <0.3 was discouraged. The conservative oxygenation group spent significantly more time with an FI_{O_2} of 0.21 (29 h vs. 1 h) and less time with a Sp_{O_2} >97% (27 h vs. 49 h) without increased time with hypoxia (Sp_{O_2} < 88%). There were no differences in the primary outcome of ventilator-free days or secondary outcomes of 90- or 180-day mortality. In a subgroup analysis, patients with hypoxemic ischemic encephalopathy treated in the conservative oxygen arm had more ventilator-free days and decreased mortality compared with the usual-care arm. No differences in cognitive function at 180 days were detected, but a significantly higher proportion of patients in the usual-care oxygen group reported severe problems with mobility and personal care. This hypothesis-generating secondary outcome suggests that exposure to higher oxygen targets and presumably hyperoxia and/or hyperoxemia could influence long-term functional outcomes and warrant further study. Importantly, there were no concerning safety issues in the conservative oxygen group, suggesting that a strategy that weans oxygen to obtain an Sp_{O_2} at or below a maximum of 96% is safe.

In the $LOCO_2$ (Liberal Oxygenation vs. Conservative Oxygenation in ARDS) trial, patients with ARDS were randomized to a conservative arterial oxygenation target (Pa_{O_2} of 55–70 mm Hg [Sp_{O_2} of 88–92%]) or a liberal target (Pa_{O_2} of 90–105 mm Hg [Sp_{O_2} ⩾ 96%]) (63). In the conservative group (n = 99), time-adjusted differences in the FI_{O_2} (−0.15), Pa_{O_2} (−28.1 mm Hg), and Sa_{O_2} (−3.8%) were all significantly lower than those of the liberal oxygenation group (n = 102). This trial was stopped early after enrollment of 205 patients because 5 patients in the conservative oxygen arm developed mesenteric ischemia. In addition, 90-day mortality, a secondary outcome, was higher in the conservative oxygenation group (44.4% vs. 30.4%; risk difference of 14.0%; 95% CI, 0.7–27.2%). As with the other trials discussed above, there was no masking of participants or clinicians to the intervention. As such, there is concern that the detection of mesenteric ischemia in the lower oxygenation target group could be biased by the lack of masking, and this is a major limitation of this trial. Early termination of this trial yielded an imprecise 90-day mortality risk difference effect estimate and casts doubt on this being a valid effect.

The recent HOT-ICU (Handling Oxygen Targets in the ICU) trial is the largest RCT of oxygen targets in critically ill patients to date (65). In this trial, 2,928 patients with hypoxemic respiratory failure receiving an FI_{O_2} of ⩾0.5 via invasive MV or receiving ⩾10 L/min oxygen in an open system were randomized to Pa_{O_2} targets of 60 mm Hg in the conservative arm versus 90 mm Hg in the liberal arm. Median values of daily mean Pa_{O_2} were 70.8 mm Hg versus 93.3 mm Hg at median FI_{O_2} levels of 0.43 and 0.56 in the conservative and liberal arms, respectively. At 90 days, 42.9% versus 42.4% of participants in the conservative versus liberal arms had met the primary outcome of 90-day mortality (risk ratio, 1.02; 95% CI, 0.94–1.11). There were no differences in secondary outcomes or serious adverse events, including conditions related to ischemia (myocardial infarction [MI], ischemic stroke, or intestinal ischemia.) Follow-up of long-term cognitive and physical function is ongoing.

The results of HOT-ICU and ICU-ROX both suggest that the choice of oxygen targets

Table 2. Randomized Trials of Conservative vs. Liberal Oxygen Targets in Critically Ill Patients

Study	Population	Sample Size	Target (Conservative vs. Liberal)	Primary Outcome	Results (Conservative vs. Liberal)
Panwar *et al.* (2016) (61)	Adult ICU patients requiring IMV	103	Sp_{O_2} of 88–92% vs. ⩾96%	Mean AUC for Sp_{O_2}, Sa_{O_2}, Pa_{O_2}, and $F_{I_{O_2}}$	Feasibility study; good separation in study groups; no adverse safety signals
Girardis *et al.* (2016) (62): OX-ICU	Adult ICU admission for >72 h anticipated (IMV and no IMV)	434	Pa_{O_2} of 70–100 mm Hg (Sp_{O_2} of 94–98%) vs. Pa_{O_2} of up to 150 mm Hg and Sp_{O_2} of 97–100%	ICU mortality	Decreased mortality; ARR, 8.6% (95% CI, 1.7–15.0%)
Mackle *et al.* (2020) (64): ICU-ROX	Adult ICU patients on IMV	1,000	Sp_{O_2} >90% with alarm set at 97%, "usual-care group"; no upper-limit alarm ($F_{I_{O_2}}$ of <0.3 discouraged)	VFD	No differences in VFD or 90- or 180-d mortality
Barrot *et al.* (2020) (63): $LOCO_2$	Adult ARDS patients on IMV	205	Pa_{O_2} of 55–70 mm Hg/Sp_{O_2} of 88–92% vs. Pa_{O_2} of 90–105 mm Hg/Sp_{O_2} of >96% for first 7 d of MV	28-d mortality	No difference in 28-d mortality; higher 90-d mortality (absolute risk increase of 7.8% [95% CI, 0.7–27.2%]). Trial stopped early for five events of mesenteric ischemia in conservative arm
Schjørring *et al.* (2021) (65): HOT-ICU	Adults with acute hypoxemic respiratory failure ($F_{I_{O_2}}$ ⩾0.5 on IMV or O_2 ⩾10 L/min in open system)	2,928	Pa_{O_2} of 60 mm Hg vs. Pa_{O_2} of 90 mm Hg	90-d mortality	No difference in 90-d mortality or other secondary outcomes; no difference in serious adverse events

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ARR = absolute risk reduction; AUC = area under the curve; CI = confidence interval; HOT-ICU = Handling Oxygen Targets in the ICU; ICU-ROX = ICU Randomized Trial Comparing Two Approaches to Oxygen Therapy; IMV = invasive MV; $LOCO_2$ = Liberal Oxygenation versus Conservative Oxygenation in ARDS; MV = mechanical ventilation; OX-ICU = Oxygen–ICU; RCT = randomized controlled trial; Sp_{O_2} = oxygen saturation as measured by pulse oximetry; TBI = traumatic brain injury; VFD = ventilator-free days.
Note this table does not include RCTs of patients with cardiac arrest, TBI, or stroke.

within narrow physiologic ranges (e.g., $Pa_{O_2} \leqslant 100$) does not significantly affect mortality in critically ill patients with respiratory failure. In contrast to the findings of the $LOCO_2$ trial, these trials support the relative safety of conservative oxygen targets. Although the conservative arm of $LOCO_2$ had a slightly lower Pa_{O_2} lower bound than HOT-ICU, both studies achieved similar Pa_{O_2} levels in the conservative group. Thus, it is unlikely that differences in the studied oxygen targets drove the difference in findings. The patient populations for each trial differed. Although all patients in the $LOCO_2$ trial had ARDS, only 12.8% patients in HOT-ICU had ARDS, and in ICU-ROX, only 65% of patients met $Pa_{O_2}/F_{I_{O_2}}$ criteria for ARDS. HOT-ICU included patients with chronic obstructive pulmonary disease (19.3%) and cardiac arrest (11.5%), and ICU-ROX included many patients with acute brain disease (40%)—all groups for whom the potential benefit of conservative oxygen targets is believed to be greater. Lastly, both HOT-ICU and ICU-ROX may have had lower proportions of patients with sepsis than $LOCO_2$. Hyperoxemia has been proposed to be potentially beneficial in sepsis, in part because of systemic vasoconstrictive effects, although a trial of 100%-$F_{I_{O_2}}$ delivery to septic patients suggested harm from this strategy (66). In addition, a *post hoc* analysis of ICU-ROX participants with sepsis did not demonstrate statistically significant differences in 90-day mortality (67). Finally, with the small

number of adverse events in $LOCO_2$ and the early cessation of trial enrollment, the observed between-group differences may have occurred by chance.

None of these trials explicitly tested targets more extreme than a Pa_{O_2} of ⩾150 mm Hg, and the largest of the trials did not include a Pa_{O_2} target above a physiologic range ($Pa_{O_2} > 100$ mm Hg). However, the small, single-center OX-ICU trial suggested that a strategy that allowed the Pa_{O_2} to range up to 150 mm Hg was inferior to Pa_{O_2} targets of 70–100 mm Hg. Randomized trials in other populations have tested oxygen supplementation strategies that have achieve supranormal targets. The HYPERS2S (Hyperoxia and Hypertonic Saline in Patients with Septic Shock) trial compared administering 100% oxygen for 24 hours with targeting normoxia (Sp_{O_2} of 88–95%) in patients with sepsis (66). Patients exposed to 100% oxygen (independent of oxygen needs) had numerically higher mortality and increased rates of ICU-acquired weakness and atelectasis compared with the normoxia group. In a *post hoc* analysis of this trial, hyperoxemia was only associated with harm in the subgroup of patients with persistently elevated lactate and hypotension (meeting Sepsis 3.0 criteria) (68). This suggests that harm may be limited to those with impaired oxygen use or delivery in the setting of septic shock. However, the *post hoc* nature of the analysis limits causal conclusions. Supraphysiologic oxygen delivery has also been studied in RCTs of normoxemic patients with acute ST-elevation MI, in which 6–8 L/min oxygen versus room air led to larger infarct size (69). In larger RCTs of patients with suspected acute MI, no differences in short- or long-term mortality were shown (70, 71). In a surgical population, the PROXI (Perioperative Oxygen Fraction) trial tested an 80% $F_{I_{O_2}}$ versus a 30% $F_{I_{O_2}}$ given for 2 hours to patients immediately postsurgery with a goal of decreasing the rates of wound infection. There was no improvement in the rates of wound infection, 30-day mortality was numerically higher in the high $F_{I_{O_2}}$ group (72), and 1-year mortality was significantly higher in the group that received a high $F_{I_{O_2}}$ (73). These randomized trials provide no support for supplementing oxygen to target supraphysiologic Pa_{O_2} levels. In addition, in those with cardiac arrest, meta-analyses provide evidence for increased mortality with this strategy (74). Although there is a small, single-center RCT and some observational studies in the traumatic brain injury literature that suggest improved functional outcomes and/or improved mortality with exposure to supraphysiologic Pa_{O_2} levels (75, 76), these findings are not consistent and are limited by methodological concerns.

Trials in critically ill adult patients also do not support or directly test a strategy of permissive hypoxemia. However, the results of randomized trials in neonates can help inform our understanding of this strategy. BOOST II (Benefits of Oxygen Saturation Targeting) and SUPPORT (Surfactant Positive Airway Pressure and Pulse Oximetry Trial) were designed to test whether or not a lower Sp_{O_2} goal (85–89% or 85–91%, respectively, vs. 91–95%) decreased the risk of retinopathy in neonatal ICU patients (77, 78). Although rates of retinopathy were indeed decreased, mortality was higher in the lower-oxygen arms. Despite being exposed to hypoxic conditions throughout gestation and being born with higher concentrations of fetal Hb with higher oxygen affinity, neonates remain vulnerable to these levels of hypoxemia. Although the implications of these trials for critically ill adults are uncertain, there is no evidence to support the use of permissive hypoxemia in adult patients.

Meta-analyses of Randomized Trials

Meta-analyses examining evidence for optimal oxygenation targets contain studies with more heterogenous populations, including patients with sepsis, stroke, cardiac arrest, or MI and patients undergoing emergency surgery. The IOTA (Improving Oxygen Therapy in Acute Illness) meta-analysis suggested that, across the included trials, conservative oxygenation targets were beneficial and decreased mortality in comparison with liberal targets (79). Furthermore, metaregression demonstrated a dose-dependent increase in mortality with a rising Sp_{O_2}. This study spurred the inclusion of an upper Sp_{O_2} limit in a subsequent guideline on use of supplemental oxygen in critically ill patients (80). A more recent meta-analysis that included the ICU-ROX and $LOCO_2$ trials showed no evidence of mortality difference or adverse effects with conservative versus liberal oxygenation strategies. However, effect sizes of a <15% relative decrease in mortality, which could still be clinically meaningful, were not ruled out (81).

Research Priorities

Several ongoing RCTs of oxygenation targets in critically ill adults may provide further guidance for oxygen dosing (NCT03537937: PILOT [Pragmatic Investigation of Optimal Oxygen Targets Trial]; NCT03287466: TOXYC [Targeted Oxygen Therapy in Critical Illness]; and ACTRN12620000391976: MEGA-ROX [The Mega Randomised Registry Trial Comparing Conservative vs. Liberal Oxygenation Targets] [82]). MEGA-ROX is a multinational trial targeting recruitment of 40,000 patients. If completed, it will be the largest trial of oxygenation targets to date and is powered to detect a 1.5% absolute difference in mortality (82). However, even if the ongoing trials establish optimal ranges of Sp_{O_2} for large groups of critically ill patients, important unanswered questions will remain. For example, regardless of the "average treatment effect" of oxygen targets across a population of critically ill adults, some patients may experience better outcomes with a lower Sp_{O_2} target (e.g., a young person with a normal Hb concentration admitted for hypoxemic ischemic encephalopathy after cardiac arrest), and some patients may experience better outcomes with a higher Sp_{O_2} target (e.g., an older person with anemia, coronary artery disease, and sepsis-induced ARDS). MEGA-ROX will have statistical power to evaluate several subgroups of interest (hypoxemic ischemic encephalopathy and sepsis, for example), although it is likely that targeted trials in other populations will be needed. For example, if a lower Sp_{O_2} range is validated as superior by MEGA-ROX, further analysis of this study and other targeted trials may need to be completed in populations such as those with trauma or critical anemia in which a lower oxygen-carrying capacity may favor higher Pa_{O_2} targets. Data from these studies could help to derive and validate estimates of the optimal Sp_{O_2} target for individual patients ("individual treatment effects") and ultimately guide clinicians toward a personalized approach to oxygen therapy in the ICU.

In addition, the effect of oxygen targets on long-term patient-important outcomes such as cognitive and physical function should be evaluated carefully. As previously

mentioned, the HOT-ICU trial has ongoing follow-up to examine physical and cognitive functioning. Given no differences in short-term outcomes in the two largest trials (HOT-ICU and ICU-ROX), a trial designed and powered specifically to assess long-term outcomes would be warranted at this time. Lastly, although trials have shown that a separation in oxygenation between groups can be maintained with different targets, arterial oxygenation frequently exceeds stated goals. This probably results from healthcare workers' tendency to react quickly when escalating therapy ($F_{I_{O_2}}$) but to react slowly when deescalating therapy (42, 43, 50). The development of safe, closed-loop systems of adjusting the delivery of supplemental oxygen may help ameliorate this problem (83), particularly once safe and optimal oxygenation targets are better defined.

Conclusions

Despite the knowledge that administering oxygen to acutely ill patients may confer both benefits and harms, we are just beginning to understand the nuances of oxygen therapy in critical illness. Although observational and trial data are inconsistent, there is accumulating evidence that targeting supranormal Pa_{O_2} levels can lead to harm. In contrast, targeting oxygen therapy to maximum Pa_{O_2} and Sp_{O_2} targets within a physiologic range appears to be safe. As one of the most widespread interventions in medicine worldwide, further optimizing oxygen therapy could have large global effects on important patient outcomes. We look forward to results of ongoing RCTs to help further guide our understanding of how to best use oxygen therapy to improve outcomes for critically ill patients. ■

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