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Oxygen Targets During Mechanical Ventilation in the ICU: A Systematic Review and Meta-Analysis

OBJECTIVES: Patients admitted to intensive care often require treatment with invasive mechanical ventilation and high concentrations of oxygen. Mechanical ventilation can cause acute lung injury that may be exacerbated by oxygen therapy. Uncertainty remains about which oxygen therapy targets result in the best clinical outcomes for these patients. This review aims to determine whether higher or lower oxygenation targets are beneficial for mechanically ventilated adult patients.

DATA SOURCES: Excerpta Medica dataBASE, Medical Literature Analysis and Retrieval System Online, and Cochrane medical databases were searched from inception through to February 28, 2021.

STUDY SELECTION: Randomized controlled trials comparing higher and lower oxygen targets in adult patients receiving invasive mechanical ventilation via an endotracheal tube or tracheostomy in an intensive care setting.

DATA EXTRACTION: Study setting, participant type, participant numbers, and intervention targets were captured. Outcome measures included “mortality at longest follow-up” (primary), mechanical ventilator duration and free days, vasopressor-free days, patients on renal replacement therapy, renal replacement free days, cost benefit, and quality of life scores. Evidence certainty and risk of bias were evaluated using Grading of Recommendations Assessment, Development and Evaluation and the Cochrane Risk of Bias tool. A random-effects models was used. Post hoc subgroup analysis looked separately at studies comparing hypoxemia versus normoxemia and normoxemia versus hyperoxemia.

DATA SYNTHESIS: Data from eight trials (4,415 participants) were analyzed. Comparing higher and lower oxygen targets, there was no difference in mortality (odds ratio, 0.95; 95% CI, 0.74–1.22), but heterogeneous and overlapping target ranges limit the validity and clinical relevance of this finding. Data from seven studies ($n = 4,245$) demonstrated targeting normoxemia compared with hyperoxemia may reduce mortality at longest follow-up (0.73 [0.57–0.95]) but this estimate had very low certainty. There was no difference in mortality between targeting relative hypoxemia or normoxemia (1.20 [0.83–1.73]).

CONCLUSIONS: This systematic review and meta-analysis identified possible increased mortality with liberal oxygen targeting strategies and no difference in morbidity between high or low oxygen targets in mechanically ventilated adults. Findings were limited by substantial heterogeneity in study methodology and further research is urgently required to define optimal oxygen therapy targets.

KEY WORDS: critical care; hyperoxia; mechanical ventilation; oxygen; oxygen therapy

Over 2 million patients receive invasive mechanical ventilation (MV) each year in the United States (20–40% of all patients admitted to ICU) at an estimated cost of \$27 billion (1, 2). As part of this treatment, all of these patients will receive supplemental oxygen to prevent hypoxemia; oxygen is one of the most commonly prescribed drugs in medicine and a lifesaving treatment for

Andrew F. Cumpstey, BMBCh^{1,2}

Alex H. Oldman, BMBS²

Daniel S. Martin, PhD^{3,4}

Andrew Smith, BMBS⁵

Michael P. W. Grocott, MD^{1,2}

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patients with respiratory failure (3). Patients requiring both MV and supplemental oxygen to treat acute lung injury have a high mortality rate of around 45% (4). MV is itself known to cause lung injury secondary to high transpulmonary pressures (“barotraumas”); alveolar overdistension (“volutrauma”); high shear forces from repeated opening and collapsing of atelectactic but recruitable lung areas (“atelectrauma”); and inflammatory injury (“biotrauma”) (5, 6). Supplemental oxygen administration in the ICU might exacerbate these processes (7).

Severe hypoxemia, common in critically ill patients, can rapidly cause irreversible tissue damage (permanent neurologic damage may result in less than 3 min [8]) and even death if not treated. Synthesis of data from contemporary studies in acutely unwell patients suggests increased harm with liberal oxygenation strategies (9–11), and there remains a paucity of high-quality evidence supporting high concentration oxygen use in the critically ill (12). Increased mortality risk associated with high F_{IO_2} , high blood oxygen levels, or both has been evidenced across many patient groups, including cardiac disease, cardiac arrest, neonatal resuscitation, stroke, and traumatic brain injury (TBI) (13–17).

Oxygen-mediated toxicity may have local or systemic effects. Local effects include absorption atelectasis; the alveolus gradually collapses as oxygen diffuses into the bloodstream during gas exchange (18). Systemic effects are thought to result from increased reactive oxygen species (ROS) production during cellular respiration (19, 20). ROS are essential for cellular signaling cascades and successful innate immune responses. However, ROS can also damage cellular structures through “oxidative stress,” resulting in inflammation and cell death (21, 22). ROS concentrations in pulmonary endothelial cells increase exponentially with hyperoxia exposure, initiating a profound inflammatory response, endothelial cell injury, capillary leak and edema formation, culminating in cell death (23). Both severe hyperoxia and longer durations of MV exacerbate severe pro-inflammatory pulmonary responses in mechanically ventilated mice (24).

It remains uncertain whether using higher oxygen targets in mechanically ventilated patients increases mortality (25) and has become increasingly urgent to understand how oxygen therapy should be targeted in these patients. In order to address whether oxygen therapy should be targeted liberally or conservatively in mechanically ventilated patients, we have conducted a systematic review and meta-analysis of all the published literature on this topic.

METHODS

This review is reported in accordance with the international Preferred Reporting Items for Systematic Reviews and Meta-Analyses (26) and was prospectively registered with the International Prospective Register of Systematic Reviews.

Search Strategies

Excerpta Medica dataBASE, Medical Literature Analysis and Retrieval System Online, and Cochrane databases were searched from the inception through to February 28, 2021. Specifically, we looked for randomized controlled trials (RCTs) containing patients receiving MV and comparing higher and lower oxygen targets between the interventional groups, but not extracorporeal membrane oxygenation, cardiac bypass, or hyperbaric oxygen. Studies looking exclusively at noninvasive ventilation or high-flow nasal oxygen with no mechanically ventilated patients at all were excluded. We considered any way of targeting oxygen as long as the aim of the study was to compare different targets between the interventional and control groups relative to each other; for example, targeting different peripheral oxygen saturation (SpO_2), Pao_2 , F_{IO_2} values, or any combination of these.

Study Selection Strategy

Titles and abstracts of potentially eligible studies were screened by two reviewers independently using Rayyan systematic review software (27). Any discrepancies for inclusion were resolved by consensus or discussed with other authors. The full text of remaining studies was then screened to determine inclusion.

Assessment of Risk of Bias in Included Studies

Risk of bias was assessed independently by two authors using criteria detailed in the Cochrane Handbook for Systematic Reviews (28). Any disagreements were either resolved by consensus or discussed with a third reviewer. Studies were assessed on:

- 1) Random sequence generation,
- 2) Allocation concealment,
- 3) Blinding of participants,
- 4) Blinding of outcome assessment,
- 5) Incomplete outcome data,
- 6) Selective reporting,
- 7) Any other biases.

Studies were classed as being low risk of bias overall when all domains were adequate and high risk of bias if one or more domains were inadequate.

Data Analysis (Including Subgroup Analysis)

Data were extracted in a standardized manner by the first reviewer, checked by the second reviewer, and discrepancies in data analysis resolved by a third reviewer if required. The primary outcome was “mortality at longest reported follow-up,” and secondary outcomes included “ICU length of stay (ICU LOS),” “duration of MV,” “vasopressor use,” “need for renal replacement therapy,” “cost benefit,” and “quality of life.”

All statistical analysis and figures were performed in RevMan Version 5.3 (Cochrane Center, Copenhagen, Denmark). A random-effects model was used for all analyses due to the expected differences in interventional groups between studies. After reviewing the selected studies, it became clear that some trials targeted significantly lower levels of oxygenation than others, meaning a “high” versus “low” comparison would be difficult to interpret as participants in some trials’ “high” oxygen groups received lower oxygenation targets than the “low” group in other studies. All authors subsequently agreed to perform two subgroup analyses to reduce the risk of clinically misleading results: one subgroup analyzed studies comparing supraphysiologic oxygen targets (“hyperoxemia”) to levels closer to those experienced during normal health (“normoxemia”) and the second subgroup contained those studies comparing normoxemia to targets lower than this (“relative hypoxemia”).

Certainty of Evidence

The principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were used to assess the quality of the body of evidence for the primary outcome, mortality at longest follow-up (29). Using this approach, the risk of within-study risk of bias (methodological quality), directness of evidence, heterogeneity of the data, precision of the effect estimates, and the risk of bias were all assessed.

RESULTS

The initial electronic search yielded 15,868 results, of which 4,792 were duplicates leaving 11,076 potential

studies. Forty-six potentially eligible studies were identified from screening these abstracts but 38 of these were ultimately excluded from the meta-analysis for different reasons (Fig. 1) on review of the full texts. One study (ICU-Randomized Trial Comparing Two Approaches to Oxygen Therapy [ROX] trial, Mackle et al [30]) was subsequently excluded after the decision to perform subgroup analysis as the oxygen targeting approach in this trial made appropriate subgroup allocation impossible (Fig. 2 and *Discussion*).

Study Characteristics

In total, the eight included studies included 4,415 participants (median, 164; range, 65–2,928; interquartile range [IQR], 95–452) who were expected to receive MV for greater than 24 hours (31); expected to remain in ICU for greater than 72 hours (32); with TBI (33, 34); with refractory septic shock (35); who had return of spontaneous circulation after out-of-hospital cardiac arrest (36); acute respiratory distress syndrome (ARDS) (37); or were receiving at least 10 L of oxygen per minute via an open system or FiO_2 greater than or equal to 0.5 via a closed system at admission to intensive care (38). Across the selected studies, the median age of reported mean participant ages was 62.6 years (IQR, 55.6–64.8 yr) and 64.1% were male (IQR, 61.8–66.0).

All included studies randomly allocated participants to “lower” or “higher” oxygenation targets; however, interventional groups were defined very differently (Fig. 2), with considerable overlap of target ranges present between studies and within individual trials. Interventional groups were defined using a prescribed FiO_2 in two studies (33, 34); using a PaO_2 target alone in two studies (36, 38), an SpO_2 target alone in one study (31), or a mixed PaO_2 and SpO_2 target in two studies (32, 37). The target ranges overlapped in one study (32). One study used an SpO_2 target of 88–95% in both groups, but the higher group received 100% oxygen ($\text{FiO}_2 = 1.0$) for the first 24 hours before reverting to this SpO_2 target for the remainder of the trial (35).

Three studies used considerably lower oxygenation targets than the other five trials, with two defining lower and higher oxygen targets as SpO_2 88–92% and SpO_2 greater than or equal to 96% (31, 37), and one using PaO_2 targets of 60 and 90 mm Hg, respectively (38). For this reason, we conducted a post hoc classification of interventions (normoxemia, hyperoxemia,

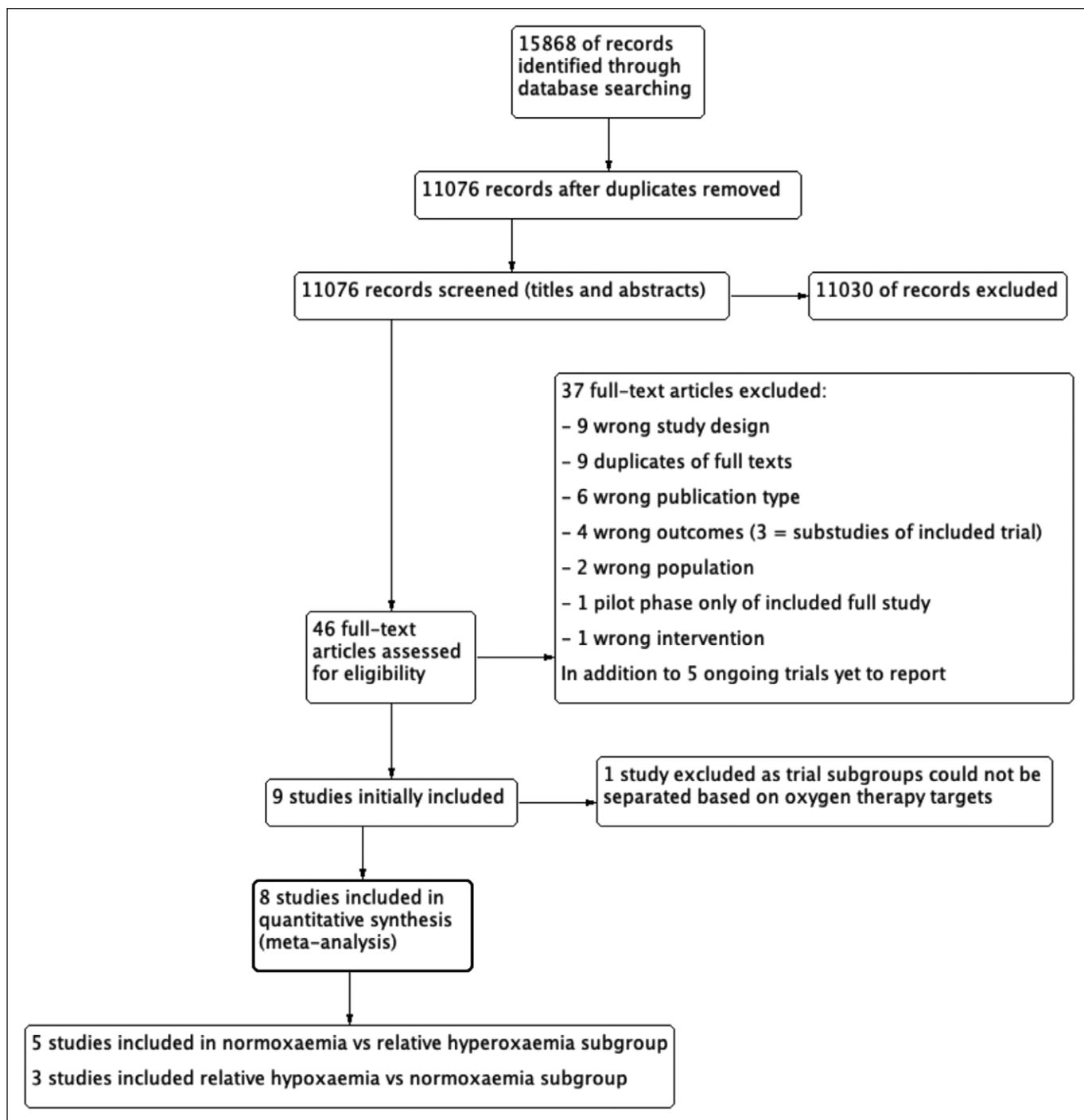


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram showing study selection and reasons for exclusion during review of full texts.

hypoxemia) defining these three trials as a subset of studies comparing normoxemia to relative hypoxemia in the analysis (31, 37), while the remaining five studies were considered to compare moderate hyperoxemia with normoxemia (32–36, 39). Hypoxemia was defined as targets encompassing arterial oxygen saturation (Sao_2) less than 92%, hyperoxemia was

defined as any of target Fio_2 greater than or equal to 0.7/ PaO_2 greater than or equal to 20 kPa/ Sao_2 greater than 96% and normoxemia was defined as intermediate targets.

The characteristics of all eight selected studies, including the different patient types and interventional oxygenation targets, are summarized in Figure 2.

Study	Country	Setting	n	Patient type	Interventional oxygenation targets		
					Lower O ₂	Intermediate	Higher O ₂
Panwar <i>et al</i> 2015	Australia New Zealand France	Multi centre	104	MV >24hrs	SpO ₂ 88 - 92%		SpO ₂ ≥ 96%
Girardis <i>et al</i> 2016	Italy	Single centre	480	ICU LOS ≥ 72hrs		PaO ₂ 70-100 mmHg SpO ₂ 94-98%	PaO ₂ < 150 mmHg SpO ₂ 97 - 100%
Taher <i>et al</i> 2016	Iran	Single centre	68	TBI		FIO ₂ = 0.5	FIO ₂ = 0.8
Asfar <i>et al</i> 2017	France	Multi centre	442	Refractory septic shock	SaO ₂ 88 - 95%		FIO ₂ - 1.0 for 24 hrs
Jakkula <i>et al</i> 2018	Finland	Multi centre	123	ROSC post OHCA		PaO ₂ 10 - 15 kPa (75 - 112.5 mmHg)	PaO ₂ 20 - 25 kPa (150 - 187.5 mmHg)
Lang <i>et al</i> 2018	Finland	Multi centre	65	TBI		FIO ₂ = 0.4	FIO ₂ = 0.7
Barrot <i>et al</i> 2020	France	Multi centre	205	ARDS	PaO ₂ 55-70 mmHg SpO ₂ 88 - 92%		PaO ₂ 90 - 105 mmHg SpO ₂ ≥ 96%
Schjørring <i>et al</i> 2021	Denmark, Switzerland, Finland, the Netherlands, UK, Iceland	Multi centre	2928	³ 10l/min O ₂ or FIO ₂ ³ 0.5	PaO ₂ = 60 mmHg		PaO ₂ = 90 mmHg
Mackle <i>et al</i> 2020	Australia New Zealand	Multi centre	1000	MV >24hrs		SpO ₂ ≥ 91 - 96% & FIO ₂ ≥ 0.21 (Lower SpO ₂ limit at clinician's discretion)	SpO ₂ ≥ 91% - no upper limit & FIO ₂ ≥ 0.3 - no upper limit (Lower SpO ₂ limit at clinician's discretion)

Figure 2. Characteristics of all nine identified studies; the eight studies included in the subgroup analysis and Mackle et al (30) (ICU-Randomized Trial Comparing Two Approaches to Oxygen Therapy trial), which we were unable to categorize because of the unique nature of the intervention. ARDS = acute respiratory distress syndrome, ICU LOS = ICU length of stay, MV = mechanical ventilation, ROSC post OHCA = return of spontaneous circulation following out-of-hospital arrest, SaO₂ = arterial oxygen saturation, SpO₂ = peripheral oxygen saturation, TBI = traumatic brain injury, UK = United Kingdom.

Risk of Bias

All studies randomly allocated participants. Using the Cochrane risk of bias tool, seven studies (88%) were considered to have adequate methods of randomization and allocation concealment (Fig. 3). Only one study was described as double blinded (33) but it was not explained how this was achieved. Attrition bias was detected in two studies (25%) (33, 34), and one trial was registered retrospectively (32). Four trials were stopped prematurely, either due to safety concerns (35, 37) or difficulty finishing recruitment (32, 34). Overall, we determined that all trials had a high risk of bias with no single study considered low risk in all assessed domains.

Primary Outcome—Mortality at Longest Follow-Up

Seven studies ($n = 4,245$ total) reported on mortality at different time points. One study reported

hospital mortality as the longest follow-up (32), one study reported 30-day mortality (36), four studies reported 90-day mortality (31, 35, 37, 38), and one study did not specify the time point of reported mortality (34). Comparing higher and lower oxygen targets, there was no difference in mortality (odds ratio [OR], 0.97; 95% CI, 0.80–1.17), but heterogeneous and overlapping target ranges, in two instances overlapping within the same study (Fig. 2), limit the validity and clinical relevance of this finding. In the post hoc subgroup analysis, targeting normoxemia was associated with a reduction in mortality in the normoxemia versus hyperoxemia subgroup comparison (OR, 0.73; 95% CI, 0.57–0.95; $n = 1,053$; $p = 0.02$; GRADE very low certainty), but mortality did not differ in the relative hypoxemia versus normoxemia subgroup comparison (OR, 1.20; 95% CI, 0.83–1.73; $n = 3,192$; $p = 0.32$; GRADE very low certainty) (Fig. 4).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Asfar 2017	+	+	-	-	+	+	-
Barrot 2020	+	?	-	-	+	+	-
Girardis 2016	+	+	-	?	+	-	-
Jakkula 2018	+	+	-	+	+	+	+
Lang 2018	?	+	-	-	-	+	-
Panwar 2015	+	+	-	?	+	+	+
Schjørring 2021	+	+	-	+	+	+	+
Taher 2016	?	?	?	?	-	?	+

Figure 3. Risk of bias summary showing authors' judgments about each risk of bias category for every included trial.

Secondary Outcomes

All secondary outcomes were also analyzed by subgroup (either normoxemia compared with hyperoxemia or normoxemia compared with relative hypoxemia).

ICU Length of Stay

In the hyperoxemia subgroup, there was no significant difference in ICU LOS (four RCTs; $n = 1,104$; mean difference, 0.97 d; 95% CI, -1.05 to 3.0; $p = 0.35$; GRADE very low certainty) (32–35). In the relative hypoxemia subgroup of studies, only one trial reported ICU LOS

with no significant difference between groups ($n = 103$; mean difference, 2.0; 95% CI, -0.28 to 4.28; $p = 0.09$; GRADE very low certainty) (31).

Duration of Mechanical Ventilation

In the hyperoxemia subgroup, two trials reported MV free days, and there was no difference in MV free days ($n = 868$; mean difference, 1.04; 95% CI, 0.63–1.46; $p < 0.001$; GRADE very low certainty) (32, 35). Two other trials in this hyperoxemia subgroup reported “average duration of MV” with no difference seen ($n = 185$; mean difference, -0.06; 95% CI, -1.54 to 1.43; $p = 0.94$; GRADE very low certainty) (34, 36).

In the relative hypoxemia subgroup, only one study reported MV free days ($n = 103$; mean difference, -1.7; 95% CI, -5.88 to 2.48; $p = 0.43$; GRADE very low certainty) (31).

Vasopressor Use

In the hyperoxemia subgroup, one trial reported vasopressor-free days ($n = 434$; mean difference, 2.0; 95% CI, -0.07 to 4.07; $p = 0.06$; GRADE very low certainty) (35, 39). In the relative hypoxemia subgroup, only one trial reported vasopressor-free days ($n = 103$; mean difference, -0.5; 95% CI, -5.37 to 4.37; $p = 0.84$; GRADE very low certainty) (31).

Need for Renal Replacement Therapy

In the hyperoxemia subgroup, one trial reported number of patients needing renal replacement therapy (RRT), ($n = 420$; OR, 0.93; 95% CI, 0.63–1.39; $p = 0.26$; GRADE very low certainty) (35).

In the relative hypoxemia subgroup, one study showed no difference in patients needing RRT ($n = 201$; OR, 1.03; 95% CI, 0.41–2.6; $p = 0.94$; GRADE very low certainty) (37). One other trial reported no difference in RRT free days ($n = 103$; mean difference, 0; 95% CI, -4.16 to 4.16; GRADE very low certainty) (31).

Cost Benefit and Quality of Life

No studies reported costs, cost benefit, or quality of life.

DISCUSSION

This systematic review and meta-analysis of eight RCTs with almost 4,500 total patients found that,

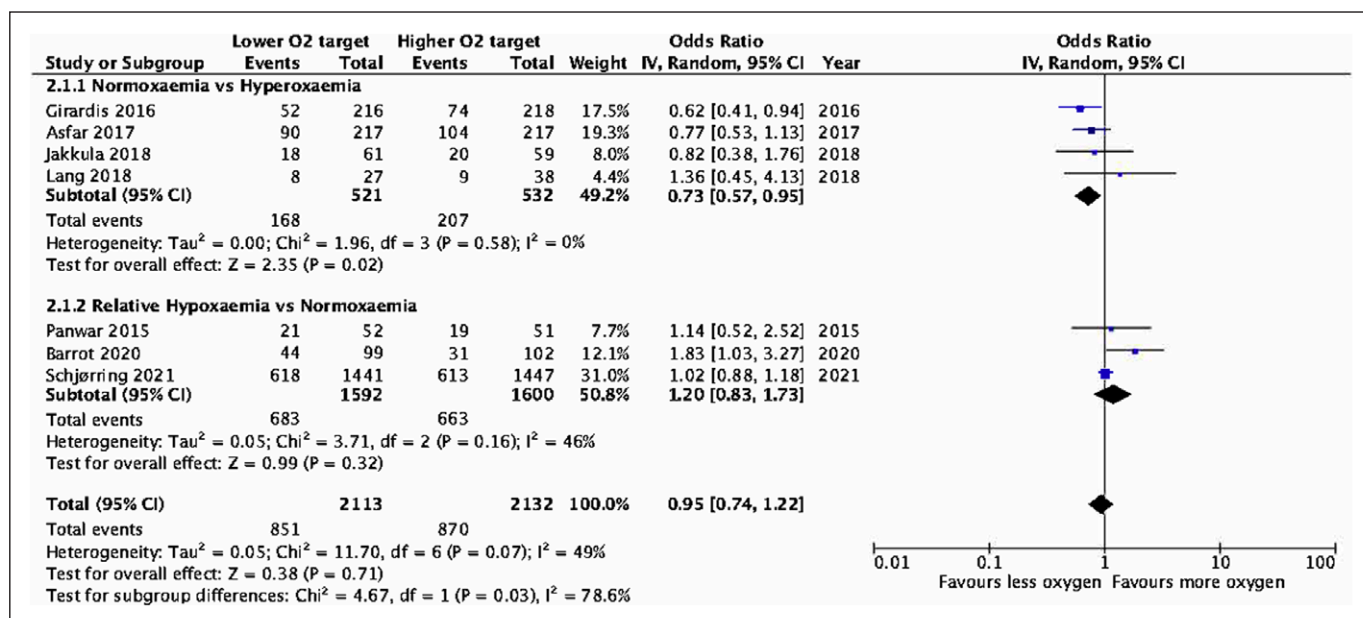


Figure 4. Mortality at longest follow-up in studies comparing normoxemia with hyperoxemia and studies comparing relative hypoxemia with normoxemia. *df* = degrees of freedom.

in mechanically ventilated adults, the highest oxygen therapy targets were associated with the highest overall mortality, although the certainty of this result is very low. Additionally, there remains uncertainty over whether higher or lower oxygen targets improved ICU LOS, duration of MV, use of vasopressor medication, use of RRT, cost benefit, or quality of life. This was hindered by the high degree of heterogeneity in study methodology and the wide variation in interventional targets (some of which were also often not achieved). There was no consistency in the type, degree, or duration of the target variable among the different trials (e.g., some studies prescribed F_{IO_2} , some targeted Sp_{O_2} values, some targeted P_{aO_2} values, and others targeted both Sp_{O_2} and P_{aO_2} values).

We performed subgroup analysis by levels of interventional oxygen in an attempt to mitigate for this effect, and as well as demonstrating an association between very liberal oxygen therapy and increased mortality, these analyses also suggested a possible trend toward increased mortality with very restrictive oxygen therapy. However, these findings are limited by the small number of trials in each subgroup and the post hoc classification of target categories (hypoxemia/normoxemia/hyperoxemia). Additionally, trials defined and reported outcomes differently. For example, one study defined MV as support with invasive or non-invasive ventilation or high-flow nasal cannula (37). One study reported adverse renal outcomes using

occurrence rate of new renal failure, while other studies reported on RRT use or “RRT free days” in the first 28 days. It was not possible to pool these different data types.

ICU-ROX was a challenging study to categorize according to targets of therapy because the stated oxygenation targets completely overlap. While other studies may have minimal overlap between oxygen therapy targets (e.g., Girardis et al [32]), there were clearly defined higher and lower target ranges. In contrast, the “conservative-oxygen” group target in the ICU-ROX study (Sp_{O_2} 91–96%) is a subset of the “usual-oxygen” group (Sp_{O_2} 91–100%). The principle distinction between groups is the additional guidance for clinicians to reduce the F_{IO_2} until 0.21 was reached if the Sp_{O_2} was above the acceptable lower limit (i.e., 91%) in the “conservative-oxygen” group, whereas for patients in the “usual-oxygen” group reducing the F_{IO_2} to less than 0.3 during MV was discouraged. In other words, the targets were largely overlapping, but the supporting guidance was different. Consequently, we were unable to justify placing the ICU-ROX trial groups in different categories based on oxygen therapy targets and therefore removed the study from the main analysis. In passing, it is notable that the time-weighted mean values achieved during this study were within the range conventionally defined as normoxia (80.25–97.5 mm Hg; 10.7–13 kPa [40]) for both groups for most of the study period (Figure S2 in supplementary appendix [39]).

The certainty of evidence was downgraded to “very low” for the primary outcome (mortality at longest follow-up) due to concerns about risk of bias, inconsistency, and imprecision. Certainty in the hypoxemia subgroup was downgraded to “low” due to concerns about risk of bias and imprecision. Only one trial was blinded (33), and four (50%) of the trials, including both studies in the “hypoxemia vs normoxemia” subgroup, were stopped prematurely (32, 34, 35, 37).

Participants also suffered from different pathologies. Two studies included patients with TBI, which might explain some methodological differences as these were the studies prescribing FIO_2 targets (33, 34). Two studies included general ICU admissions expected to be ventilated for greater than 24 (31) or greater than 72 hours (32); one study included patients following out-of-hospital arrest (36); one septic shock (35); and one only patients with ARDS (37). It therefore remains unclear whether different pathologies may benefit from different oxygenation targets.

In 2018, a large systematic review of over 16,000 acutely ill patients demonstrated that liberal oxygen increased mortality and concluded that more conservative oxygen therapy (not targeting above SpO_2 94–96%) should be encouraged in this cohort (11). This review included four of the same studies included in our meta-analysis (31–33, 35), and their findings are consistent with studies associating hyperoxemia with worse outcomes in other patient groups; including those with myocardial infarction and stroke (14, 41).

However, less high-quality evidence of this effect exists specifically in patients admitted to intensive care. A recent systematic review in this cohort concluded that great uncertainty remained about whether higher FIO_2 affected mortality, lung injury, and other adverse events due to insufficient evidence (25). Equally, another systematic review was unable to support or refute the beneficial effects of lower oxygen targets in mechanically ventilated patients as no studies comparing normoxemia to permissive hypoxemia could be identified despite comprehensive searches (42).

High FIO_2 , and both high and low Pao_2 within the first 24 hours of ICU admission have all retrospectively been associated with worse mortality (43), supporting the concept for needing more precise control of arterial oxygenation in critically ill patients (19). Our subgroup analyses might support this view and are consistent with a proposed “U-shaped” relationship

between oxygenation and mortality (19), with trends toward lowest mortality in the normoxemic group in each subgroup analysis. This finding must be treated cautiously though, being nonsignificant in one subgroup and very low certainty in the other. However, another large systematic review (> 200,000 patients total) would also support this hypothesis, retrospectively associating both excessively low and high Pao_2 values with increased mortality in ICU (10). However, 16 of the 17 studies in this review were observational, so interventional evidence remains lacking. Similarly, it remains unclear exactly where the nadir of this curve might sit, or indeed given that this “optimum value” is unlikely to be the same point in all critically ill patient groups, which groups would benefit from slightly more or slightly less oxygen therapy and by how much?

CONCLUSIONS

This systematic review and meta-analysis (8 RCTs, > 4,000 patients) an increase in overall mortality with very high oxygen targets in critically unwell adults receiving invasive MV. This study highlights the significant heterogeneity in methodology into oxygen research in critical care. Oxygen remains fundamental to all aspects of medicine, but particularly to patients requiring ventilatory support. Given the high numbers of patients receiving MV and supplemental oxygen internationally, further research is urgently needed if the best evidence-based quality of care is to be provided for our sickest patients in the intensive care setting.

- 1 *Perioperative and Critical Care Theme, National Institute of Health Research (NIHR) Southampton Biomedical Research Centre, University Hospital Southampton / University of Southampton, Southampton, United Kingdom.*
- 2 *Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom.*
- 3 *Intensive Care Unit, Royal Free Hospital, Pond Street, London, United Kingdom.*
- 4 *Peninsula Medical School, University of Plymouth, John Bull Building, Derriford, Plymouth, United Kingdom.*
- 5 *Lancaster Patient Safety Research Unit, University Hospitals of Morecambe Bay NHS Foundation Trust, Kendal, United Kingdom.*

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Edwards Lifesciences and Deltex Medical; he is also a Director of Oxygen Control Systems and Chief Investigator on the U.K. Randomized Trial Comparing Two Approaches to Oxygen Therapy (ROX) trial. Dr. Grocott is a director of Oxygen Control Systems; he has received honoraria for speaking and/or travel expenses from British Oxygen Company Medical (Linde Group), AstraZeneca, Edwards Lifesciences, and Cortex GmbH; he leads the Xtreme Everest Oxygen Research Consortium and the Fit-4-Surgery research collaboration; he serves as the U.K. NIHR Clinical Research Network national specialty group lead for Anesthesia Perioperative Medicine and Pain and is an elected council member of the Royal College of Anaesthetists; and he is also co-investigator on the U.K. ROX trial. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: mike.grocott@oton.ac.uk

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