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Cumpstey, AF

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Oxygen targets during mechanical ventilation in the intensive care unit – a systematic review & meta-analysis

Andrew F. Cumpstey, BMBS^{1,2}, Alex H. Oldman, BMBS², Daniel S. Martin, PhD^{3,4}, Andrew Smith, BMBS⁵, Michael P. W. Grocott, MD^{1,2}

1. *Critical Care Research Group, Southampton National Institute of Health Research, Biomedical Research Centre, University Hospital Southampton, Southampton, UK.*
2. *Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK.*
3. *Intensive care unit, Royal Free Hospital, Pond Street, London NW3 2QG, UK.*
4. *Peninsula Medical School, University of Plymouth, John Bull Building, Derriford, Plymouth, PL6 8BU, UK.*
5. *Lancaster Patient Safety Research Unit, University Hospitals of Morecambe Bay NHS Foundation Trust, Kendal, UK*

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Corresponding author:

Professor Mike Grocott

Professor of Anaesthesia and Critical Care Medicine

University of Southampton and University Hospital Southampton

Tremona Road

Southampton SO16 6YD

United Kingdom

Phone: +44 (0)23 8120 8449

e-mail: mike.grocott@soton.ac.uk

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Abstract

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 which 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

EMBASE, MEDLINE and Cochrane medical databases were searched from inception through to 28th February 2021.

Study Selection

Randomised 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 & risk of bias were evaluated using GRADE & the Cochrane Risk of Bias tool. A random effects models was used, and subgroup analysis looked separately at studies comparing hypoxaemia vs normoxaemia and normoxaemia vs hyperoxaemia.

Data Synthesis

Data from 8 trials (4415 participants) were analysed. Data from 7 studies (n=4245) demonstrated targeting normoxaemia compared to hyperoxaemia may reduce mortality at longest follow up (Odds Ratio 0.73, [95% Confidence Interval 0.57 to 0.95]) but this estimate had very low certainty. There was no difference in mortality between targeting relative hypoxaemia or normoxaemia (1.20 [0.83 to 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.

Introduction

Over 2 million patients receive invasive mechanical ventilation each year in the USA (20-40% of all patients admitted to intensive care, 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 hypoxaemia; oxygen is one of the most commonly prescribed drugs in medicine and a lifesaving treatment for patients with respiratory failure (3). Patients requiring both mechanical ventilation and supplemental oxygen to treat acute lung injury have a high mortality rate of around 45% (4). Mechanical ventilation is itself known to cause lung injury secondary to high transpulmonary pressures ('barotrauma'); alveolar overdistension ('volutrauma'); high shear forces from repeated opening and collapsing of atelectatic but recruitable lung areas ('atelectrauma'); and inflammatory injury ('biotrauma') (5, 6). Supplemental oxygen administration in the ICU might exacerbate these processes (7).

Severe hypoxaemia, common in critically ill patients, can rapidly cause irreversible tissue damage (permanent neurological damage may result in less than three minutes (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 inspired oxygen fraction (FIO_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 (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 blood stream 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 signalling 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 oedema formation, culminating in cell death (23). Both severe hyperoxia and longer durations of mechanical ventilation 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 (PRISMA) (26), and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42020183367).

Search strategies

EMBASE, MEDLINE and Cochrane databases were searched from the inception through to 28th February 2021. Specifically, we looked for randomised controlled trials containing patients receiving mechanical ventilation 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 non-invasive 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; e.g. targeting different peripheral oxygen saturation (SpO₂), PaO₂, FIO₂ 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 were 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 was extracted in a standardised 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 'intensive care length of stay (ICU LOS)', 'duration of mechanical ventilation', '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 centre, 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' vs '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 analysed studies comparing supra-physiological oxygen targets ('hyperoxaemia') to levels closer to those experienced during normal health ('normoxaemia'); and the second subgroup contained those studies comparing normoxaemia to targets lower than this ('relative hypoxaemia').

Certainty of evidence

The principles of the 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 4792 were duplicates leaving 11,076 potential studies. 46 potentially eligible studies were identified from screening these abstracts but 38 of these were ultimately excluded from the meta-analysis for different reasons (see Figure 1) on review of the full texts. One study (ICU ROX trial, Mackle *et al* 2020 (30)) was excluded after the decision to perform subgroup analysis as the oxygen targeting approach in this trial made appropriate subgroup allocation impossible (see Figure 2 and Discussion).

Study characteristics

In total, the eight included studies included 4415 participants (median 164, range 65 to 2928, Interquartile Range (IQR) 95 to 452) who were expected to receive mechanical ventilation for >24 hours (31); expected to remain in ICU for >72 hours (32); with traumatic brain injury (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 litres of oxygen per minute via an open system or $\text{FIO}_2 \geq 0.5$ via a closed system on admission to intensive care (38). Across the selected studies, the median age of reported mean participant ages was 62.6 years (IQR 55.6 to 64.8), and 64.1% were male (IQR 61.8 to 66.0).

All included studies randomly allocated participants to 'lower' or 'higher' oxygenation targets; however, interventional groups were defined very differently (see Figure 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 $\text{SpO}_2 \geq 96\%$ (31, 37), and one using PaO_2 targets of 60 and 90 mmHg respectively (38). For this reason, we conducted a post-hoc classification of interventions (normoxaemia, hyperoxaemia, hypoxaemia) defining these three trials as a subset of studies comparing normoxaemia to relative hypoxaemia in the analysis (31, 37), whilst the remaining five studies were considered to compare moderate hyperoxaemia with normoxaemia (32–36, 39). Hypoxaemia was defined as targets encompassing $\text{SaO}_2 < 92\%$, hyperoxaemia was defined as any of target $\text{FiO}_2 \geq 0.7$ / $\text{PaO}_2 \geq 20\text{KPa}$ / $\text{SaO}_2 > 96\%$ and normoxaemia was defined as intermediate targets.

The characteristics of all 8 selected studies, including the different patient types and interventional oxygenation targets, are summarised in Figure 2.

Risk of bias

All studies randomly allocated participants. Using the Cochrane risk of bias tool, 7 (88%) studies were considered to have adequate methods of randomization and allocation concealment (see Figure 3). Only one study was described as double blinded (33) but it was not explained how this was achieved. Attrition bias was detected in 2 (25%) of studies (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=4245 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). Targeting normoxaemia was associated with a reduction in mortality in the normoxaemia vs. hyperoxaemia subgroup (Odds Ratio (OR) 0.73, 95% Confidence Interval (CI) [0.57 to 0.95], n = 1053, p = 0.02; GRADE very low certainty), but mortality did not differ in the relative hypoxaemia vs normoxaemia subgroup (OR 1.20, 95% CI [0.83 to 1.73], n = 3192, p = 0.32; GRADE low certainty) See Figure 4.

Secondary outcomes

All secondary outcomes were also analysed by subgroup (either normoxaemia compared to hyperoxaemia, or normoxaemia compared to relative hypoxaemia).

Intensive care length of stay

In the hyperoxaemia subgroup, there was no significant difference in intensive care length of stay (ICU LOS) (4 RCTs, n = 1104, mean difference 0.97 days, 95% CI [-1.05 to 3.0], p = 0.35, GRADE very low certainty)(32–35). In the relative hypoxaemia 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 hyperoxaemia subgroup, two trials reported mechanical ventilation (MV) free days and there was no difference in MV free days (n = 868, mean difference 1.04, 95% CI [0.63 to 1.46], p < 0.001, GRADE very low certainty) (32, 35). Two other trials in this hyperoxaemia subgroup reported 'average duration of mechanical ventilation' (MV duration) 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 hypoxaemia 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 hyperoxaemia 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 hypoxaemia 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 hyperoxaemia subgroup, one trial reported number of patients needing renal replacement therapy (RRT), (n = 420, OR 0.93, 95% CI [0.63 to 1.39], p = 0.26, GRADE very low certainty) (35).

In the relative hypoxaemia subgroup, one study showed no difference in patients needing RRT (n = 201, OR 1.03, 95% CI [0.41 to 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 randomised controlled trials with almost 4500 total patients found that, 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 mechanical ventilation, use of vasopressor medication, use of renal replacement therapy, 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 amongst the different trials (e.g. some studies prescribed FIO₂, some targeted SpO₂ values, some targeted PaO₂ values and others targeted both SpO₂ and PaO₂ 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 towards 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 (hypoxaemia / normoxaemia / hyperoxaemia). Additionally, trials defined and reported outcomes differently. E.g. One study defined mechanical ventilation as support with invasive or non-invasive ventilation, or high flow nasal cannulae (37). One study reported adverse renal outcomes using incidence of new renal failure, whilst 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 categorise according to targets of therapy because the stated oxygenation targets completely overlap. Whilst other studies may have minimal overlap between oxygen therapy targets (e.g. Girardis 2016 (32)), there were clearly defined higher and lower target ranges. In contrast, the "conservative-oxygen" group target in the ICU-ROX study (SpO₂ 91 to 96%) is a subset of the "usual-oxygen" group (SpO₂ 91% to 100%). The principle distinction between groups is the additional guidance for clinicians to reduce the FIO₂ until 0.21 was reached if the SpO₂ was above the acceptable lower limit (i.e. 91%) in the "conservative-oxygen" group, whereas for patients in the "usual-oxygen" group reducing the FIO₂ to less than 0.3 during mechanical ventilation 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 mmHg; 10.7-13 kPa (40)) for both groups for most of the study period (see 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 hypoxaemia 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 'hypoxaemia vs normoxaemia' subgroup, were stopped prematurely (32, 34, 35, 37).

Participants also suffered from different pathologies. Two studies included patients with traumatic brain injury, which might explain some methodological differences as these were the studies prescribing FIO₂ targets (33, 34). Two studies included general ICU admissions expected to be ventilated for >24 (31), or >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 SpO₂ 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 hyperoxaemia 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 FIO₂ 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 normoxaemia to permissive hypoxaemia 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 towards lowest mortality in the normoxaemic group in each subgroup analysis. This finding must be treated cautiously though, being non-significant 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, >4000 patients) an increase in overall mortality with very high oxygen targets in critically unwell adults receiving invasive mechanical ventilation. 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 mechanical ventilation 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.

References

1. Wunsch H, Linde-Zwirble WT, Angus DC, et al.: The epidemiology of mechanical ventilation use in the United States*. *Critical Care Medicine* 2010; 38:1947–1953
2. Wunsch H, Wagner J, Herlim M, et al.: ICU Occupancy and mechanical ventilator use in the United States [Internet]. *Crit Care Med* 2013; 41[cited 2020 May 9] Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3840149/>
3. O’Driscoll BR, Smith R: Oxygen Use in Critical Illness. *Respir Care* 2019; 64:1293–1307
4. Phua J, Badia JR, Adhikari NKJ, et al.: Has Mortality from Acute Respiratory Distress Syndrome Decreased over Time? *Am J Respir Crit Care Med* 2009; 179:220–227
5. Beitler JR, Malhotra A, Thompson BT: Ventilator-Induced Lung Injury. *Clin Chest Med* 2016; 37:633–646
6. Slutsky AS: Lung Injury Caused by Mechanical Ventilation. *CHEST* 1999; 116:9S-15S
7. Sinclair SE, Altemeier WA, Matute-Bello G, et al.: Augmented lung injury due to interaction between hyperoxia and mechanical ventilation*. *Critical Care Medicine* 2004; 32:2496–2501
8. Leach RM, Treacher DF: Oxygen transport—2. Tissue hypoxia. *BMJ* 1998; 317:1370–1373
9. Page D, Ablordeppey E, Wessman BT, et al.: Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study. *Critical Care* 2018; 22:9
10. Damiani E, Adrario E, Girardis M, et al.: Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. *Critical Care* 2014; 18:711
11. Chu DK, Kim LH-Y, Young PJ, et al.: Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *The Lancet* 2018; 391:1693–1705
12. Oldman AH, Cumpstey AF, Martin DS, et al.: Data integrity issues: catalyst for a more robust approach to research on perioperative oxygen therapy? *Perioperative Medicine* 2019; 8:7
13. McNulty PH, King N, Scott S, et al.: Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *American Journal of Physiology - Heart and Circulatory Physiology* 2005; 288:H1057–H1062
14. Stub D, Smith K, Bernard S, et al.: Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. *Circulation* 2015; 131:2143–2150

15. Kilgannon J, Jones AE, Shapiro NI, et al.: Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010; 303:2165–2171
16. Mazdeh M, Taher A, Torabian S, et al.: Effects of Normobaric Hyperoxia in Severe Acute Stroke: a Randomized Controlled Clinical Trial Study. *Acta Medica Iranica* 2015; 676–680
17. Davis DP, Meade W, Sise MJ, et al.: Both Hypoxemia and Extreme Hyperoxemia May Be Detrimental in Patients with Severe Traumatic Brain Injury. *Journal of Neurotrauma* 2009; 26:2217–2223
18. Munshi L, Ferguson ND: Evolving Issues in Oxygen Therapy in Acute Care Medicine. *JAMA* 2020; 323:607–608
19. Martin DSBs, Grocott MPWM: Oxygen Therapy in Critical Illness: Precise Control of Arterial Oxygenation and Permissive Hypoxemia*. *Critical Care Medicine* 2013; 41:423–432
20. Lumb AB, Walton LJ: Perioperative Oxygen Toxicity. *Anesthesiology Clinics* 2012; 30:591–605
21. Cumpstey A, Feelisch M: Free Radicals in Inflammation. In: Cavaillon J-M, Singer M, editor(s). *Inflammation: From Molecular and Cellular Mechanisms to the Clinic*, 4 volume set. Wiley; 2017. p. 695–726.
22. Sies H: Oxidative stress: a concept in redox biology and medicine. *Redox Biol* 2015; 4:180–183
23. Kaestle S, Brueckl C, Habazettl H, et al.: Sequential formation of reactive oxygen species by mitochondria and NAD(P)H oxidase in lung endothelial cells during hyperoxia. *The FASEB Journal* 2006; 20:A725–A726
24. Helmerhorst HJF, Schouten LRA, Wagenaar GTM, et al.: Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. *Intensive Care Medicine Experimental* 2017; 5:27
25. Barbateskovic M, Schjørring OL, Krauss SR, et al.: Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit [Internet]. *Cochrane Database of Systematic Reviews* 2019; [cited 2020 Mar 14] Available from: <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012631.pub2/full>
26. Moher D, Liberati A, Tetzlaff J, et al.: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [Internet]. *PLoS Med* 2009; 6[cited 2020 Jun 26] Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2707599/>

27. Ouzzani M, Hammady H, Fedorowicz Z, et al.: Rayyan—a web and mobile app for systematic reviews [Internet]. *Syst Rev* 2016; 5[cited 2020 Jun 26] Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5139140/>
28. Higgins JPT, Altman DG, Gotzsche PC, et al.: The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928–d5928
29. Guyatt GH, Oxman AD, Vist GE, et al.: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336:924–926
30. The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med* 2020; 382:989–998
31. Panwar R, Hardie M, Bellomo R, et al.: Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. *Am J Respir Crit Care Med* 2015; 193:43–51
32. Girardis M, Busani S, Damiani E, et al.: Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial [Internet]. *JAMA* 2016; [cited 2016 Oct 9] Available from: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.11993>
33. Taher A, Pilehvari Z, Poorolajal J, et al.: Effects of Normobaric Hyperoxia in Traumatic Brain Injury: A Randomized Controlled Clinical Trial [Internet]. *Trauma Mon* 2016; 21[cited 2020 Mar 14] Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4869427/>
34. Lång M, Skrifvars MB, Siironen J, et al.: A pilot study of hyperoxemia on neurological injury, inflammation and oxidative stress. *Acta Anaesthesiologica Scandinavica* 2018; 62:801–810
35. Asfar P, Schortgen F, Boissramé-Helms J, et al.: Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial. *The Lancet Respiratory Medicine* 2017; 5:180–190
36. Jakkula P, Reinikainen M, Hästbacka J, et al.: Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Med* 2018; 44:2112–2121
37. Barrot L, Asfar P, Mauny F, et al.: Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *New England Journal of Medicine* 2020; 382:999–1008
38. Schjørring OL, Klitgaard TL, Perner A, et al.: Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure [Internet]. *New England Journal of Medicine* 2021; [cited 2021 Mar 1] Available from: <https://www.nejm.org/doi/10.1056/NEJMoa2032510>

39. The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Supplementary Appendix for Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *New England Journal of Medicine* 2020; 382:989–998
40. Williams AJ: Assessing and interpreting arterial blood gases and acid-base balance. *BMJ* 1998; 317:1213–1216
41. Rincon F, Kang J, Maltenfort M, et al.: Association between hyperoxia and mortality after stroke: a multicenter cohort study. *Crit Care Med* 2014; 42:387–396
42. Gilbert-Kawai ET, Mitchell K, Martin D, et al.: Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients [Internet]. In: Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd; 2014. [cited 2016 Oct 6] Available from:
<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009931.pub2/abstract>
43. de Jonge E, Peelen L, Keijzers PJ, et al.: Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008; 12:R156

Figures

Figure 1. PRISMA flow diagram showing study selection and reasons for exclusion during review of full texts

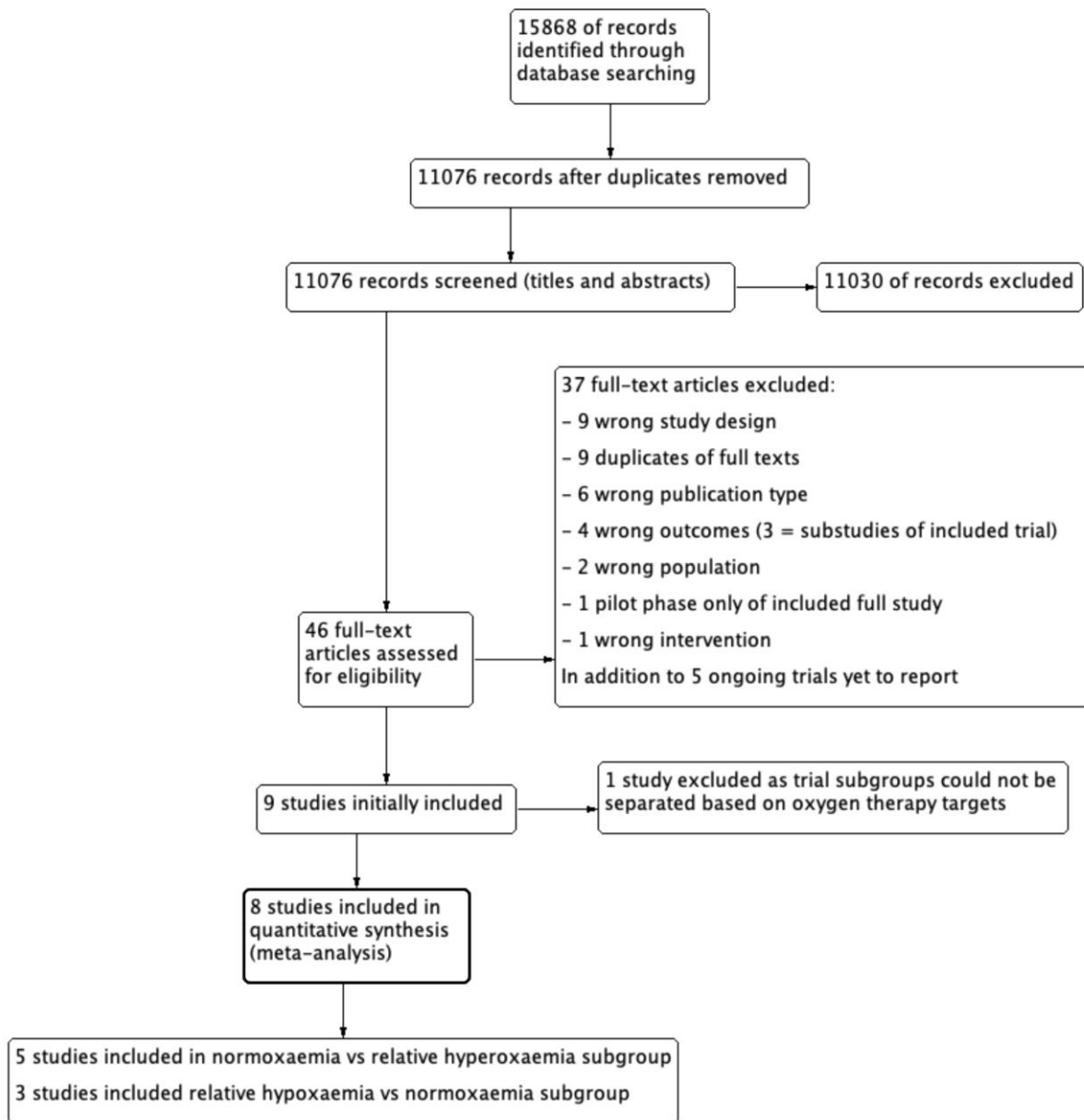


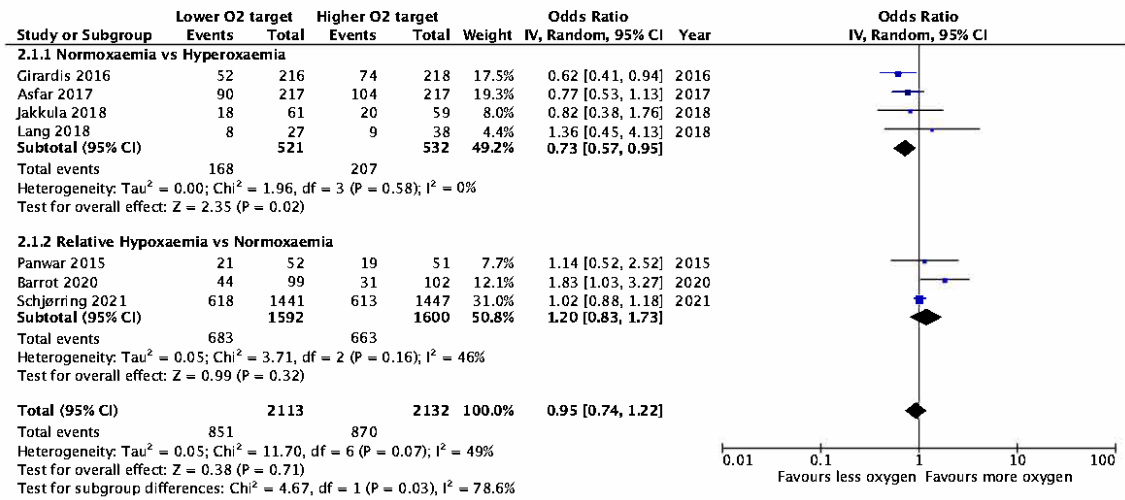
Figure 2. Characteristics of all 9 identified studies; the 8 studies included in the subgroup analysis and Mackle et al 2020 (ICU ROX trial), which we were unable to categorise because of the unique nature of the intervention. (MV = mechanical ventilation, ICU LOS = intensive care length of stay, TBI = traumatic brain injury, ROSC post OOH = return of spontaneous circulation following out of hospital arrest, ARDS = acute respiratory distress syndrome).

Study	Country	Setting	n	Patient type	Interventional oxygenation targets		
					Lower O ₂	Intermediate	Higher O ₂
Panwar et al 2015	Australia New Zealand France	Multi centre	104	MV >24hrs	SpO ₂ 88 - 92%		SpO ₂ ≥ 96%
Girardis et al 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 et al 2016	Iran	Single centre	68	TBI		FIO ₂ = 0.5	FIO ₂ = 0.8
Asfar et al 2017	France	Multi centre	442	Refractory septic shock	SaO ₂ 88 - 95%		FIO ₂ - 1.0 for 24 hrs
Jakkula et al 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 et al 2018	Finland	Multi centre	65	TBI		FIO ₂ = 0.4	FIO ₂ = 0.7
Barrot et al 2020	France	Multi centre	205	ARDS	PaO ₂ 55-70 mmHg SpO ₂ 88 - 92%		PaO ₂ 90 - 105 mmHg SpO ₂ ≥ 96%
Schjørring et al 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 et al 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 3. Risk of bias summary showing authors' judgments about each risk of bias category for every included trial

	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 4. Mortality at longest follow up in studies comparing normoxaemia with hyperoxaemia, and studies comparing relative hypoxaemia with normoxaemia



Appendix

Search strategies:

MEDLINE

- 1 exp Critical Illness/ or exp Critical Care/ or exp intensive care units/ or exp Emergency Medicine/ or exp Emergency Service, Hospital/
- 2 (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or critically ill or critical illness or acutely ill or intensive care or critical care or ICU* or ITU*).tw.
- 3 ("cardiac bypass" or ECMO or extracorporeal or "heart?lung bypass" or hyperbaric).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 4 1 or 2
- 5 4 not 3
- 6 Oxygen/ or exp Oxygen-Inhalation-Therapy/ or exp Hyperoxia/
- 7 (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2 or oxygen* or conservative or liberal or restrictive).mp.
- 8 6 or 7
- 9 5 and 8
- 10 Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/
- 11 ((clinical adj trial\$) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or PLACEBOS/ or placebo\$.tw. or randomly allocated.tw. or (allocated adj2 random\$).tw.
- 12 10 or 11
- 13 case report.tw. or letter/ or historical article/
- 14 12 not 13
- 15 9 and 14

EMBASE

- 1 exp Critical Illness/ or exp Critical Care/ or exp intensive care units/ or exp Emergency Medicine/ or exp Emergency Service, Hospital/
- 2 (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or critically ill or critical illness or acutely ill or intensive care or critical care or ICU* or ITU*).tw.

- 3 ("cardiac bypass" or ECMO or extracorporeal or "heart?lung bypass" or hyperbaric).mp.
[mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
- 4 1 or 2
- 5 4 not 3
- 6 Oxygen/ or exp Oxygen-Inhalation-Therapy/ or exp Hyperoxia/
- 7 (hyperoxia or hyperoxemia or hyperoxaemia or hypoxia or hypoxemia or hypoxaemia or anoxia or anoxemia or anoxaemia or arterial oxygen or high oxygen or oxygenat* or blood gas or oxygen saturation or pao2 or sao2 or spo2 or fio2 or oxygen* or conservative or liberal or restrictive).mp.
- 8 6 or 7
- 9 5 and 8
- 10 Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or randomized controlled trial.pt. or multicenter study.pt. or clinical trial.pt. or exp Clinical Trials as topic/
- 11 ((clinical adj trial\$) or ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3))).tw. or PLACEBOS/ or placebo\$.tw. or randomly allocated.tw. or (allocated adj2 random\$).tw.
- 12 10 or 11
- 13 case report.tw. or letter/ or historical article/
- 14 12 not 13
- 15 9 and 14

Cochrane CENTRAL

- #1 MeSH descriptor: [Hyperoxia] explode all trees
- #2 MeSH descriptor: [Oxygen] this term only
- #3 MeSH descriptor: [Oxygen Inhalation Therapy] explode all trees
- #4 ((inspiratory or fraction or supplementary or concentration) near oxygen)
- #5 hyperoxia or hyperaemia or arterial oxygen or oxygenation or spo2 or fio2 or pao2
- #6 #1 or #2 or #3 #4 or #5
- #7 MeSH descriptor: [Critical Care] explode all trees
- #8 MeSH descriptor: [Critical Illness] explode all trees
- #9 MeSH descriptor: [Intensive Care Units] explode all trees
- #10 (emergency department* or ED or emergency room* or ER or high dependency unit* or HDU or prehospital* or critically ill or acutely ill or intensive care or critical care or ICU*):ti,ab,kw
- #11 #7 or #8 or #9 or #10

- #12 (bypass or ECMO or extracoporeal or hyperbaric or heart?lung):ti,ab,kw
- #13 #11 not #12
- #14 #6 and #13