VIEWPOINT

Oxygen Targets in Critically Ill Patients: Let's be Cautiously Liberal

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Introduction

Supplemental oxygen is often provided to patients in the intensive care unit (ICU). The cells utilize oxygen to generate energy; any hypoxemia affects cellular metabolism, and in turn, leads to organ failures. On the contrary, excess oxygen (hyperoxemia) is equally dangerous. The oxygen delivery to tissues drops when the partial pressure of oxygen (PaO_2) falls below 60 mm Hg (oxygen-hemoglobin dissociation curve), which is monitored by arterial oxygen saturation (SpO_2) by pulse oximetry at the bedside. So, any transient respiratory compromise may subject patients to episodes of severe hypoxia when low oxygen levels are targeted. Similarly, targeting lower SpO_2 with the fear of hyperoxemia may lead to lesser oxygen delivery to an already compromised oxygen delivery secondary to shock or anemia or both, a scenario that is not infrequent in ICU. On the contrary, studies have shown that hyperoxemia causes vasoconstriction, reduces cardiac output and heart rate, and reduces coronary and cerebral perfusion.[1] Also, excess oxygen supplementation can lead to free radical-mediated injury (e.g., reperfusion) when it depletes the antioxidant stores, which may aggravate organ injuries, especially in the brain and heart.

Thus, optimal delivery of oxygen is desired, but the safe PaO_2 target range is not known, and there is no consensus yet on the PaO_2 levels to define normoxia and hyperoxia. It is accepted that the PaO_2 between 60 and 90 mm Hg is safe, values below 60 mm Hg are not safe, but the upper limit of PaO_2 above which it is associated with adverse events is not known. Previous studies have shown that PaO_2 levels above 120 mm Hg (previous studies tested >150–300 mm Hg, this range is not targeted clinically nowadays) are associated with adverse outcomes.[2] In normalcy, a healthy individual can't have a PaO_2 of >100 mm Hg without oxygen supplementation, just breathing room air. So, any PaO_2 >100 mm Hg may be considered excess, but there are no high-quality studies to prove it. Moreover, identifying or monitoring hyperoxia is not easy at the bedside, as SpO_2 of 100% may reflect PaO_2 levels of >90–100 mm Hg and may not be useful to detect hyperoxia. It is not a common practice to actively reduce the oxygen delivered to target lower PaO_2, yet when the patient is on lower oxygen needs, say fractional inspired SpO_2 [fraction of inspired oxygen (FiO_2)] of 30–40%.

Oxygen targets in critically ill patients are still controversial, and many observational studies have shown increased adverse outcomes with both hypoxia and hyperoxia but with varied cutoffs. Recently a retrospective study analyzing two large ICU databases (electronic ICU—chronic respiratory disease and medical information mart for intensive care-III) showed a U-shaped relationship between increased adverse events with both hypoxia and hyperoxia.[3] The optimal cutoff for oxygen found was SpO_2 levels between 94 and 98%. They compared the adverse event rates based on the amount of time spent within this cutoff. The adverse events were lesser when the time spent was >80% compared to 40%. A recent study (hyperoxemia in postsurgical sepsis, N = 454) where the secondary analysis of postoperative septic shock patients showed increased organ dysfunction, ICU length of stay, and ventilation days in patients with PaO_2 <100 mm Hg.[4] The above studies though, favor a little higher oxygen target, can't conclude a causal relationship.

There are many randomized control trials (RCT) that were performed to answer the optimal PaO_2 in the recent past but with varied PaO_2/SpO_2 cutoffs and outcomes, leading to difficulty in the interpretation of results and performing a meta-analysis. A feasibility study by Panwar et al. (CLOSE study) showed that it is feasible and relatively safe to target lower PaO_2 of around 70 mm Hg in mechanically ventilated patients, opening the gate for further studies on this topic.[5] In 2016, a single center RCT (oxygen ICU, N = 480) compared SpO_2 of 94–98% (70–100 PaO_2) versus 98–100% (up to 150 mm Hg) in mechanically ventilated patients showed lesser mortality with the conservative oxygen group, 11.6% versus 20.2%.[6] The median PaO_2 was 102 [interquartile range (IQR), 88–116] versus 87 mm Hg (IQR,79–97) in the liberal versus conservative groups, respectively. Though the results were promising, the trial included fewer sick patients, and it was stopped prematurely after an unplanned interim analysis (there can be an exaggerated effect size) and had high bias (no blinding, reporting, and other bias). On the contrary, a multicenter study, The liberal oxygenation versus conservative oxygenation in acute respiratory distress syndrome (ARDS) ($LOCO_2$, 13 centers, N = 205), done in France, compared 55–70 mm Hg (SpO_2, 88–92%)

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with 90–105 mm Hg (SpO_2 ≥96%) in patients with ARDS.[7] The levels were maintained up to 7 days from randomization. The study was stopped prematurely due to no benefit and more mesenteric ischemia in the conservative group. In another trial that was published at the same time in 2020, the ICU-ROX (N = 1000) compared the SpO_2 levels of <97% (91–96%, with FiO_2 >21%) versus usual (SpO_2 >91%, no restriction of oxygen and SpO_2).[8] The intervention was continued till day 28. It didn't show any differences in the primary outcome, ventilator-free days on day 28, and 90-day mortality or cognitive function. The actual targets achieved were PaO_2 of 70–100 mm Hg versus 80–110 mm Hg, so there was an overlap. This study was pragmatic in a sense it targeted SpO_2, which is more feasible at the bedside rather than PaO_2. Another multicenter study done across 35 centers in European ICUs, named handling oxygenation targets in the ICU study (HOT-ICU, N = 2928), included only patients with acute hypoxic respiratory failure defined as either need of 10 L of oxygen or 50% FiO_2 and hypothesized that lower PaO_2 would reduce mortality.[9] They compared the PaO_2 60 mm Hg versus 90 mm Hg, which was maintained for 90 days. The actual targets achieved were median (IQR) PaO_2 of 70.8 mm Hg (66.6–76.5) versus 93.3 (87.1–98.7) and median (IQR) SpO_2 of 93% (94–95) versus 96% (95–97). There was no difference in mortality at 90 days between the lower and higher oxygen target groups (42.9 versus 42.4%). Moreover, the secondary outcomes like ventilation-free days, the occurrence of new episodes of stroke, myocardial infarction, and intestinal ischemia were also similar between groups. This is the largest study to date, which showed both targets were safe without any major adverse events in contrast to previous studies, the oxygen ICU and $LOCO_2$.

Many meta-analysis and systemic reviews have been done with varied objectives and with contrasting results. The international ovarian tumor analysis meta-analysis (In 2018, 25 RCTs and N = 16,037) involving varied patient populations (stroke, myocardial infarction, critically ill, sepsis, and emergency surgical) showed mortality benefits with conservative oxygen strategy.[10] In this analysis, only two RCTs were on critically ill patients, and the rest of them were non-critically ill. Among the critically ill (oxygen ICU and CLOSE), the oxygen ICU study influenced the results, which was a single center, stopped prematurely and had a high bias. A subgroup of postsurgical patients showed better outcomes with the liberal oxygen group. Chen et al., in meta-analysis (seven RCTs that had long follow-ups, N = 5265), divided patients based on the severity of hypoxia (PaO_2/FiO_2 ratio) into mild, moderate, and severe hypoxemia, defined as PaO_2/FiO_2 of >200 mm Hg, 100–200 mm Hg, and <100 mm Hg, respectively.[11] There was no statistically significant difference in mortality or any of the secondary outcomes when analyzed all together, but further sensitivity analysis showed the subgroup of patients with PaO_2/FiO_2 ratio >100 mm Hg (i.e., mild-moderate hypoxia) benefited from conservative oxygen targets. Zhao et al. performed a network meta-analysis of RCTs (eight trials, N = 2532) and classified oxygen targets into trinary [conservative (PaO_2, 55–90 mm Hg); moderate (PaO_2, 90–150 mm Hg); and liberal (PaO_2, >150 mm Hg)] and quadruple classification [liberal, moderate, and conservative (PaO_2, 70–90 mm Hg) and far conservative (PaO_2, 55–70 mm Hg)] and analyzed 30-day mortality, ICU and 90-day mortality.[12] There was no difference between any groups in both classifications. Further analysis with the surface under the cumulative ranking curve scores and survival curves showed moderate targets (PaO_2, 90–150 mm Hg) in trinary classification and conservative (PaO_2, 70–90 mm Hg) in quadruple classification might be superior to the liberal and far conservative groups. This study emphasizes the benefit of staying away from extreme values that may be detrimental. A recent systemic review (eight RCTs, N = 4415) divided the studies into two groups, hypoxemia versus normoxemia and normoxemia versus hyperoxemia showed increased mortality with a liberal group which was influenced by the oxygen ICU study, which had a higher bias, and stopped prematurely.[13] There was more heterogenicity, high bias, and inclusion of low-quality studies. The overall analysis of all studies together didn't favor any group.

Recent RCTs and subsequent meta-analysis have shown its safe if the PaO_2 is between 60–70 and 90–100 mm Hg in nonselected critically ill patients, and there is no data to show the safety of long-term effects. Later, the authors of both ICU-ROX and HOT-ICU studies published the subgroup and predefined analysis of long-term outcomes of oxygen supplementation. Later, 1-year follow-up of patients of the HOT-ICU study showed no difference in mortality or health-related quality of life at 1 year.[14] Later, a secondary Bayesian analysis which was performed to analyze the heterogeneous effect of oxygen supplementation among all patients, didn't show any benefit with the lower oxygen target. Interestingly, in patients with shock requiring noradrenaline, there was increased mortality with increased noradrenaline dose in the lower oxygen group with odds of 1.67 (0.92–3.04), but it may need further evaluation. *Post hoc* analysis of ICU-ROX study in patients with suspected hypoxic brain injury analyzed whether the conservative oxygen strategy would decrease death or unfavorable neurological outcome at 180 days after adjusting for baseline variables that predict outcome in cardiac arrest patients.[15] The analysis showed a trend of less unfavorable neurological outcomes (55.1% versus 68.1%) and death at 180 days (43% versus 59%) in a conservative group but was not statistically significant. But it showed more vasopressor and ventilator-free days with the lower oxygen target group compared to the higher target group.

These studies reflect that the oxygen target should be different for a different group of critically ill patients and the safe zone lie between the PaO_2 of 60–70 and 90–110 mm Hg with a higher margin still debatable. The range beyond these values isn't well studied in clinical studies, and it is better to avoid it in critically ill patients (Fig. 1). Even though there are no studies that have shown any clear benefit of any PaO_2 range, from logical reasoning, we can use the safer range that has been well studied in clinical settings. Most studies (RCTs) have either shown benefit or no harm or are comparable to lower oxygen targets with PaO_2 targets of 80–100 mm Hg (Fig. 1). Only a few studies in a defined population (hypoxic brain injury, myocardial infarction where there is an increased chance of free radical-mediated tissue damage due to reperfusion) benefit from lesser PaO_2 around 80 mm Hg. In real life, we achieve lesser than what we target, given an example while dosing for dialysis or providing calories or protein. So, a lower target may unknowingly lead to still lower PaO_2 levels that may be detrimental. Nevertheless, the safety margin is higher with higher oxygen targets (e.g., PaO_2, 80–90 mm Hg). Future studies may throw some light and hope there occurs a consensus on the value range of normoxia, hypoxia, and hyperoxia for both clinical and research settings.

Hyperoxia may be dangerous, and effects may not be immediate, but hypoxia can kill and is always detrimental. So better be more cautious and be a little more liberal in targeting oxygen while managing critically ill patients. Let us be cautiously liberal!

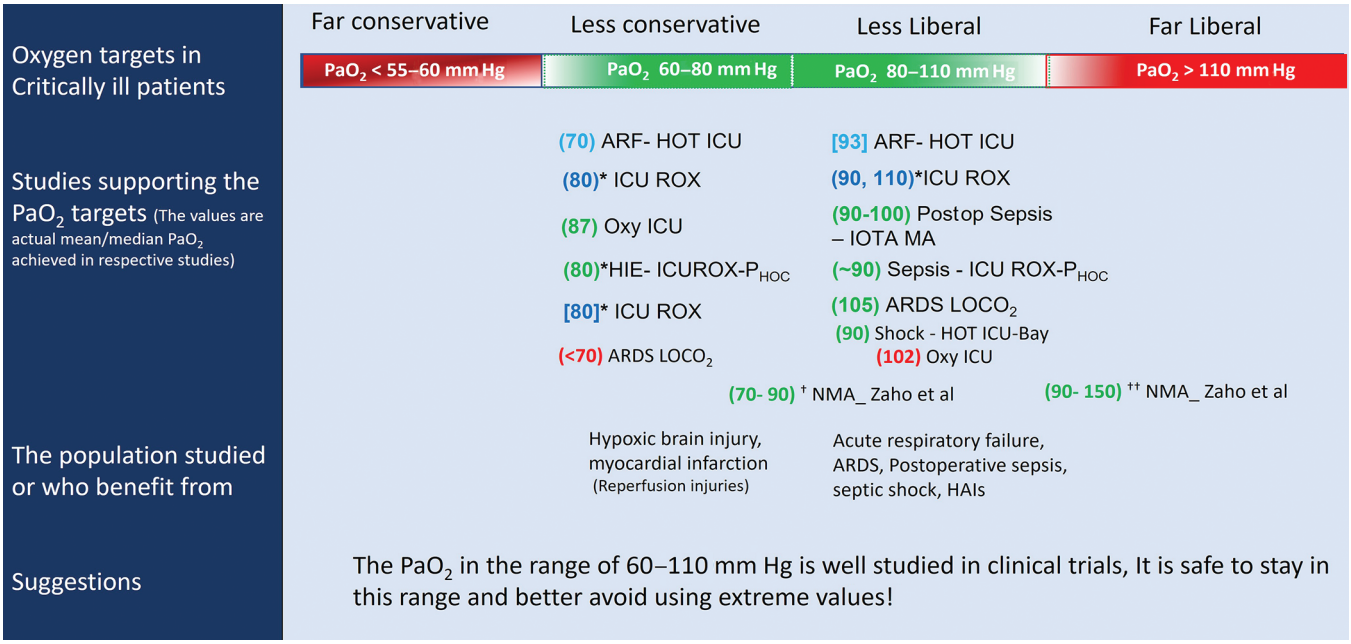

Fig. 1: Summary of oxygen targets studies in critically ill patients. Only the randomized controlled trials are included. See the text for information and refer respective studies for further details. Majority of studies showed benefit with PaO_2 >80 mm Hg, favoring less liberal approach. ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; Bay, Bayesian analysis; HAI, hospital acquired infections; NMA, network meta-analysis; PaO_2, partial pressure of oxygen; the values inside the bracket are median PaO_2 values achieved in the trials. Green color— benefit was shown in the study, blue— no difference between two groups, red— study had shown harm with that strategy, *mean values, ~approximately, †better than PaO_2 of 55–70 mm Hg, ††better than PaO_2 of >150 mm Hg

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