COMMENTARY

Oxygen Targets in Critical Illness: Commentary on the Pro–Con Debate

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Supplemental oxygen therapy is one of the most commonly used intensive care unit (ICU) therapies. The primary aim of oxygen therapy is to prevent hypoxia. Oxygen was considered easily available, cheap, and safe. The coronavirus disease 2019 pandemic proved otherwise.

Normal arterial partial pressures of oxygen (PaO_2) levels are between 80 and 100 mm Hg. A PaO_2 level of <60 mm Hg is generally considered to be the lower limit of acceptable oxygenation. Several adaptive mechanisms are triggered in hypoxia.[1] Downregulation of mitochondrial uncoupling has been demonstrated in human volunteers[2] to enable more efficient adenosine triphosphate generation and ensure mitochondrial protection. There is a release of hypoxia-inducible factors and activation of glycolytic enzymes, leading to a preponderance of anaerobic metabolism.[2] Mitochondrial hibernation is another suggested mechanism to reduce oxygen demand. Other mechanisms that allow acclimatization are hypoxic pulmonary vasoconstriction, increased cardiac output, polycythemia, and increased production of 2,3-diphosphoglycerate with a shift of the oxygen dissociation curve to the right, allowing oxygen offloading to the tissues.[3] Oxygen toxicity has been known and studied from the time of its discovery.[4] Hyperoxia increases the production of toxic reactive oxygen species, which can cause injury in the lungs through absorption atelectasis and poor mucociliary clearance, and retinal and central nervous system damage by necrosis or apoptosis. Supranormal PaO_2 also leads to a fall in the cardiac output due to generalized vasoconstriction and increased afterload, causing coronary vasoconstriction and predisposing to myocardial ischemia. Hypoxia, on the contrary, kills as well. This makes an optimal oxygen target in critically ill patients very debatable.

The argument in favor of conservative oxygen targets stems from the fear of hyperoxemia-induced oxygen toxicity. The author discussed the oxygen–ICU[5] trial, which showed lower mortality in the conservative oxygen group in comparison to conventional targets. The author also cited the HYPER2S[6] trial, which found higher mortality in septic shock patients with hyperoxia. The author summarized the IOTA meta-analysis[7] of 16,000 patients, which confirmed increased mortality in adult acutely ill patients with hyperoxia. The author looked at studies on specific patient populations,[8,9] such as postcardiac arrest survivors, hypoxic-ischemic encephalopathy, acute myocardial infarction,[10] and acute respiratory distress syndrome (ARDS) showing detrimental effects in patients with hyperoxia.

The liberal/cautious approach to oxygen targets, as the author chose to call it, rests on the fear of extreme harm in hypoxia. The author cited the liberal or conservative oxygen therapy

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($LOCO_2$)[11] trial in ARDS patients, which not only demonstrated no mortality benefit, but also an increase in adverse events, such as mesenteric ischemia in the conservative group. The author cited the failure of studies, such as the HOT–ICU12 trial and the ICU-ROX[13] trial to prove the benefit of conservative oxygen targets on clinical end points, including mortality, ventilator-free days, and the incidence of adverse events, such as intestinal ischemia, myocardial ischemia, etc.

Several randomized controlled trials have been published, comparing conservative with liberal oxygenation strategies in the recent past with contradictory outcomes. Conducting such trials is challenging because of several reasons. In critically ill patients, different strategies are used for oxygen supplementation. Fraction of inspired oxygen (FiO_2) values are adjusted continuously to ensure that the PaO_2 remains within a target range. However, it is not possible to monitor the PaO_2 continuously. So, arterial saturation is measured by pulse oximetry, which calibrates well with the PaO_2 in general but not in critically ill patients with severe hypotension, ARDS, etc. Regional perfusion abnormalities cannot be measured easily, and so the effects of the same on patient outcomes cannot be predicted. Thus, even with similar study interventions and patient populations, small differences in the implementation and monitoring of the titration protocol or case mix alter trial results significantly.[6]

There are several differences in key trials.

For example, the ICU-ROX[13] studied a broad cohort of patients undergoing mechanical ventilation, whereas the $LOCO_2$[11] trial enrolled only patients with ARDS. Patients in the $LOCO_2$[11] trial had worse gas exchange impairment, requiring higher FiO_2 levels and longer periods of support with mechanical ventilation. Thus, patients in the $LOCO_2$[11] trial may have been more prone to hypoxemia, especially in the conservative oxygen group. In the $LOCO_2$[11] trial, the target peripheral oxygen saturation (SpO_2) level was at least 96% in the control group, whereas the control group in ICU-ROX[13] was usual care, in which clinicians may have used lower targets. In the

ICU-ROX[13] study, the conservative strategy target SpO_2 was 90– 96%, while in the $LOCO_2$[11] trial, the target was 88–92%. With a target oxygen level as low as 88%, patients in the conservative oxygen group in the $LOCO_2$[11] trial were potentially more prone to hypoxemia. And because the target ranges for the two groups were closer in ICU-ROX,[13] the opportunity to detect any difference was potentially reduced. In the HOT–ICU[12] study, with a lower partial pressure of oxygen (PO_2) target group of 60 mm Hg and a higher target group of 90 mm Hg, although the lower (PO_2) group did not fare better, the patients were older in comparison to the $LOCO_2$[11] trial, included almost 20% of patients with COPD, and reported overall higher mortality. Although the target was 60, the median PO_2 in the lower target group was 70.8 mm Hg.

In a meta-analysis[14] including eight trials with about 4,400 patients in 2022, authors found high heterogeneity, inconsistencies, and biases in the trials. They divided patients into three groups. Hypoxia (SpO_2 < 92%), hyperoxia (SpO_2 > 96%), and an intermediate group (SpO_2 92–96%). They found no difference in mortality between higher and lower oxygen targets (odds ratio, 0.95; 95% confidence interval, 0.74–1.22),[14] but commented that heterogeneity and overlapping target ranges in the trials limited the validity and clinical relevance of the findings.

To conclude, a nuanced, personalized approach to oxygen supplementation in patients undergoing mechanical ventilation is the way forward. It is clear that no patient needs hyperoxia. The upper limit of safety is unknown but probably is a PO_2 of 110–150 mm Hg. Permissive hypoxia may not be permissible because lower limits are not known. It is prudent to not administer supplemental oxygen when the SpO_2 is 96% or greater. The lower range of the SpO_2 target in any conservative strategy, especially in patients requiring a high level of F_IO_2, should probably be 90% and not 88%. Special patient populations, such as acute brain pathologies, traumatic brain injury, cerebrovascular accidents, and sepsis probably benefit from higher targets. The parameters that may help assess the adequacy of oxygen delivery[15] include lactate levels, central venous oxygen saturation (>70%), central venous to arterial partial pressure of carbon dioxide ($PaCO_2$) difference (<6 mm Hg), the ratio between the central venous and arterial venous $PaCO_2$ difference, and the arterial to central venous PaO_2 difference[15]. Future trials will have to address how a particular target is set and achieved in each group and how the consequences of a particular target affect particular patients and particular organ injuries. The upper limit of safe oxygenation remains unestablished. The MEGA ROX trial will probably answer some of the unanswered questions.

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