Oxygen supplementation targets in patients with acute respiratory failure

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Many critically ill patients require oxygen supplementation, but the best level of support remains uncertain. The trade-off involves adequate oxygen delivery to tissues versus oxygen toxicity, which can result in adverse outcomes. The target level of support often involves measurement of either the PaO_2 or the peripheral O_2 saturation with a goal of 60 mmHg for PaO_2 and 90% for O_2 saturation. This level of support typically places the patient on the plateau region of the hemoglobin-oxygen dissociation curve with the argument that additional increments in PaO_2 or O_2 saturation provide little additional O_2 content.

Potential adverse effects of hyperoxia include formation of reactive oxygen species that can cause direct tissue injury, disruption of surfactant function, and absorptive atelectasis in regions along with low VQ ratios.[1–3] These latter regions may contribute to the development of atelectrauma and additional lung injury. *The New England Journal of Medicine* recently published two randomized control trials that compared conservative oxygen supplementation versus a liberal or usual oxygen supplementation.

The ICU-ROX (Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy) trial investigators randomized 1000 adult patients who were expected to require mechanical ventilation beyond the initial day of recruitment to either conservative or usual oxygen therapy.[4] In both groups the default limit for the lower O_2 saturation was 90%; in the conservative oxygen group the upper limit of peripheral O_2 saturation target was 97%. If the patients in the conservative group maintained adequate O_2 saturations, then the FiO_2 could be reduced as low as 0.21. The number of days of mechanical ventilation in survivors was approximately 3 in both groups. The primary outcome was the number of ventilator-free days from randomization until day 28, and there was no difference between the 2 groups. The mean duration of ventilator-free days was 21.3 days in the conservative group and 22.1 days in the usual care group. The conservative care group spent more time at an FiO_2 of 0.21 (median 29 hours) than the usual care group (1 hour) and spent less time with O_2 saturations exceeding 96% than the usual care group (27 hours vs. 49 hours). Mortality rates at 90 and 180 days were similar. These investigators concluded that conservative oxygen therapy did not significantly affect the number of ventilator-free days and presumably did not reduce any potential adverse effects of oxygen on lung function and mechanics or on systemic tissues.

The $LOCO_2$ (Liberal Oxygenation versus Conservative Oxygenation in Acute Respiratory Distress Syndrome) trial investigators randomized patients with ARDS to a conservative oxygen therapy target or to a liberal oxygen therapy target.[5] The conservative target was a PaO_2 of 55 to 70 mmHg and O_2 saturations of 88 to 92%. The liberal target was a PaO_2 90 to 105 mmHg and O_2 saturations ≥96%. This study initially planned to include 850 patients, but the trial was stopped after the recruitment of 205 patients due to safety concerns. Initial baseline characteristics of the patients included respiratory system compliance of approximately 30 ml/cm H_2O and PaO_2/FiO_2 ratios of 117–120. Most patients (71%) required catecholamine support. There were definite differences in the FiO_2, PaO_2, and O_2 saturation between the 2 groups over 7 days. After day 1, the FiO_2 was approximately 40% in the conservative oxygenation group and 55% in the liberal oxygenation group. There was no difference in mortality at 28 days, but there was an increase in mortality in the conservative oxygen cohort at 90 days. Five patients in the conservative oxygen therapy group had mesenteric ischemia events, but details about these patients were not provided. These investigators concluded that a conservative oxygen

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therapy with a goal target goal of 55 to 70 mmHg did not increase survival at 28 days. Potential hazards associated with lower targets included intermittent hypoxemia and possibly decreased O_2 delivery to tissue beds with lower perfusion.

van den Boom et al reviewed two large databases to determine, if possible, optimal oxygen saturation targets in critically ill patients.[6] This study included 26,723 patients from an ICU collaborative research database and 8,564 patients from a medical information mart for intensive care database. Patients were included if they had at least 48 hours of oxygen therapy and 24 pulse oximetry O_2 saturation measurements. The investigators analyzed the median O_2 saturations and their association with hospital mortality. These results had a U-shaped distribution, and the optimum median O_2 saturation was in the range of 94 to 98%. There was increased mortality below 94% and increased mortality above 98%. The mortality increased with the percent time spent outside the optimal range. These results were adjusted for age, gender, BMI, the sequential organ failure score (SOFA) on admission, and the duration of oxygen therapy.

Other studies have reported adverse outcomes associated with hyperoxemia. Page et al retrospectively reviewed the outcomes of patients intubated for mechanical ventilation in an emergency department.[7] This study focused only on the PaO_2s in the emergency department and required patients to have normoxia (PaO_2 60 to 120 mmHg) during the first day in the ICU. Three hundred and fifty patients had normoxia in the emergency department, and 300 had hyperoxia (i.e., a PaO_2 >120 mmHg). Time spent in the emergency department was approximately 5.5 hours. After adjustment for multiple variables, they determined that hyperoxia in the emergency department was associated with increased mortality; the overall mortality rate was 29.7% in the hyperoxia group and 19.4% in the normoxia group. There was a gradient effect with increasing levels of hyperoxia resulting in increased mortality.

Asfar and colleagues studied hyperoxia and hypertonic saline in patients with septic shock using a 2×2 factorial randomized clinical trial.[8] The oxygen management strategy involved either an FiO_2 of 1.0 for the first 24 hours or an FiO_2 set to target hemoglobin oxygen saturation at 88 to 95%. This trial was stopped prematurely for safety reasons after 442 patients had been recruited. At 28 days and 90 days an increased number of patients in the hyperoxia group had died, but this did not reach statistical significance. There was an increased number of total adverse events during this study in the hyperoxia group and an increased number of patients with atelectasis. There is a trend towards an increased frequency of ICU acquired weakness in the hyperoxia cohort. This study was reanalyzed using a Sepsis-3 criteria for septic shock.[9] Patients in the hyperoxia group with septic shock requiring vasopressors who had lactate levels greater than 2 mmol/L had higher mortality at 28 days (57.4% versus 44.3%, $P = 0.054$). Multivariate analysis of these results indicated that there was an independent association between hyperoxia and mortality at 28 days and 90 days in patients with septic shock with high lactate levels.

In summary, a retrospective review of a very large database suggested that the optimal O_2 saturation in critically ill patients requiring O_2 supplementation was 94 to 98%. Two randomized controlled trials did not find any benefit in patients who had a lower upper limit of peripheral O2 saturation (97%) to limit hyperoxemia or a target PaO_2 of 55 to 70 mmHg. These studies suggest that oxygen supplementation targets should include O_2 saturations greater than 94% and less than 98%. However, other a relatively large studies demonstrated that hyperoxia in the emergency department during the initial phase of mechanical ventilation and hyperoxia for the first 24 hours of mechanical ventilation resulted in increased mortality. These results lead to some uncertainty as to the best strategy for oxygen supplementation in critically ill patients.

Correlation does not imply causation. There are plausible reasons why patients with high O_2 saturation might do worse that do not involve O_2 toxicity. High O_2 saturation might be due to infrequent attention to clinical status. Patients with high O_2 saturation might require greater levels of O_2 support which may indicate a higher acuity or severity of disease irrespective of attempts to control for disease severity. Retrospective analyses and particularly meta-analyses may provide the basis for good hypotheses to be tested, but these hypotheses should be tested by prospective clinical trials designed to explicitly answer the question.

Clinicians frequently do not know the stability of O_2 saturation in critically ill patients, the frequency of low values, the frequency of high values, and the duration of either low or high values. In addition, clinicians usually do not know which organs have decreased perfusion and consequently are more vulnerable to low O_2 saturations that might result in critical reductions in O_2 delivery. Consequently, the management of oxygenation needs to be individualized according to the patient's clinical status and gas exchange, and there is no substitute for frequent reassessment of critically ill patients. Oxygen therapy probably needs more attention than it frequently receives in ICUs, given other critical care patient management responsibilities in ICUs. An FiO_2 of 1.0 should be used for the shortest period of time possible. Hyperoxemia should be avoided in patients post cardiac arrest, in patients with CNS trauma, and in patients who are post stroke.[10] The target of peripheral O2 saturation should exceed 90% and possibly be in the range of 94 to 98%. Patients with low O_2 saturations and high FiO_2s warrant extra concern and may need changes in management strategies, if possible.

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