

Supplemental oxygen or something else?

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The acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemia and inflammatory damage to the alveolar-capillary barrier, and can be caused by primary damage to the epithelium (pulmonary ARDS) or the endothelium (extrapulmonary ARDS) (1). Once ARDS is recognized, supplemental oxygen is one of the first therapeutic approaches used to rapidly increase alveolar ($P_{A}O_2$), arterial (PaO_2), and venous (PvO_2) partial pressures of oxygen. On the other hand, the risks associated with hyperoxia, such as resorption atelectasis and oxygen toxicity, must be considered (2). The negative effects of higher fractions of inspired oxygen (FiO_2) must be recognized independent of higher PaO_2 values. Therefore, in this editorial, we propose to discuss the relationship between unnecessary hyperoxia with high FiO_2 levels, PaO_2 and SpO_2 targets during mechanical ventilation, and optimal cutoffs for PaO_2 or FiO_2 in different clinical conditions.

One longitudinal analysis of previous data from 10 clinical trials, published between 1996 and 2013, sought to determine whether cumulative oxygen exposure that resulted in $PaO_2 >80$ mmHg (goal) 5 days after enrollment was associated with higher mortality rates at day 90 in ARDS patients (3). The authors found that oxygen exposure resulting in PaO_2 above the protocol goal occurred frequently and was indeed associated with higher 90-day mortality; the data showed that this association may not be explained by reverse causality. In other words,

severe patients required more oxygen. However, this cannot explain the increased mortality. The nature of retrospective studies of administrative data precludes any inference of causation. In addition, those patients with high FiO_2 exposure also showed higher plateau pressure, positive end-expiratory pressure (PEEP) levels, and worse hemodynamics, which suggest disease severity regardless of FiO_2 levels. Thus, it is unknown whether oxygen supplementation alone had a significant effect on clinical outcomes.

Aggarwal *et al.* raise an important question about liberal *versus* conservative oxygen supplementation. A recent prospective randomized parallel-group trial showed that using a conservative FiO_2 within a range of 0.21–0.80 to achieve the assigned targets of 88–92% SpO_2 , compared to 96% SpO_2 for the liberal oxygenation group, did not cause harm (4). In a before-and-after study, a conservative oxygenation strategy (target SpO_2 of 90–92%) was associated with lower incidence of new organ dysfunction (5). It seems clear that FiO_2 should not be fixed, but rather titrated to achieve PaO_2 or SpO_2 targets. There is no reason to keep FiO_2 high when SpO_2 is 100%, or in specific circumstances such as comorbid chronic obstructive pulmonary disease and ARDS. Conversely, fixed FiO_2 levels have been advocated by World Health Organization (WHO) for use in the intraoperative and postoperative periods (6), with a view to reducing the incidence of surgical

site infection. This expected beneficial effect must be weighed against the negative effects of supplemental oxygen therapy, such as oxidative stress, which may amplify the inflammatory response. As stated in the British Thoracic Society guidelines for oxygen use (7), a fixed level of FiO_2 should not be the goal in mechanically ventilated patients, instead; oxygen should be prescribed to a target SpO_2 or PaO_2 range.

The Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) trial, conducted during 4 consecutive weeks in the winter of 2014 in a convenience sample of 459 ICUs from 50 countries across 5 continents (8), showed an inverse relationship between FiO_2 and SpO_2 , suggesting that clinicians increased FiO_2 to treat hypoxemia, aiming to achieve a target PaO_2 level. In other words, supplemental oxygen therapy was not used liberally. In this line, a recent systematic review and meta-analysis of more than 16,000 acutely ill adults showed that liberal supplemental oxygen was harmful (9). In ARDS, FiO_2 may have consequences on oxygenation index due to the degree of shunt, and therefore may jeopardize early clinical recognition of the syndrome. In this line, LUNG SAFE trial reported that ARDS was found to be underdiagnosed (60.2%). According to the Berlin definition guideline, the $\text{PaO}_2/\text{FiO}_2$ ratio should be used at the time of ARDS onset to stratify its severity. Previous observational studies have found that FiO_2 predicts mortality (10). In future clinical trials, standardized ventilator settings could be used instead to better stratify ARDS severity. A previous study (11) showed reduced utility of $\text{PaO}_2/\text{FiO}_2$ ratio to stratify ARDS severity at the time of diagnosis due to non-standardized ventilator settings. The authors proposed that ARDS recognition should be a two-step process, whereby initial assessment at ARDS onset (or detection) would be followed by a second assessment 24 h later, under standardized ventilator settings. This would represent a better method for optimizing risk stratification.

One of the most important ventilator settings to be standardized is the FiO_2 level. Since high FiO_2 levels may affect clinical outcome, unnecessarily high FiO_2 levels should be avoided. It is widely accepted that oxygen toxicity emerges at FiO_2 values higher than 0.5–0.6 (12). However, these values were obtained in humans with normal lungs (13), and are thus not representative of respiratory diseases, in which the threshold for oxygen toxicity in the lungs is lower, precluding any extrapolation of safe oxygen levels in critically ill patients. The decrease in FiO_2 in the presence of high PaO_2 values is not so as

prompt as the increase of FiO_2 in the presence of low PaO_2 values (14).

In addition to concentration of oxygen, the duration of oxygen supplementation is also an important parameter to be controlled. In fact, previous studies have shown that increased duration of exposure to excess oxygen was associated with a worsening of oxygenation index (15), although this remains controversial (16). With modern ventilators that enable capture of 24-h windows and visualization of parameter trends, duration of exposure to given oxygen concentrations can be easily tracked.

There is a clear disconnection between offering oxygen to achieve normal PaO_2 levels at bedside and the consequence of high levels of oxygen exposure due to the production of reactive oxygen species (ROS) within the respiratory chain in the mitochondria. In the clinical setting, it is almost impossible to obtain ROS data, whereas PaO_2 is readily measured. Previous studies have shown that a clinically tolerable FiO_2 (0.6) can trigger increased rates of mitochondrial superoxide anion (O_2^-) production and release of hydrogen peroxide (H_2O_2) from lung mitochondria, suggesting that $\text{FiO}_2 > 0.6$ exceeds a threshold of mitochondrial antioxidant defenses (17). In ARDS, this consequence can be amplified, as ROS production is already higher due to the lung inflammatory process (18).

In ARDS, hypoxemia can be caused by the alveolar component of the shunt coming from non-ventilated and/or hypoventilated alveoli, the so-called “right-to-left shunt” (19). Non-ventilated areas are unresponsive to higher FiO_2 , while hypoventilated areas will increase their P_AO_2 levels and could inhibit hypoxic pulmonary vasoconstriction, further impairing blood-gas exchange. This phenomenon has been evaluated using mathematical models (20) and observed in experimental (21) and clinical studies (22), and is proportional to the degree of shunt. In the setting of high FiO_2 values, oxygen toxicity may emerge as resorption atelectasis (23), impairment of airway smooth muscle cell proliferation (24), induction of bronchopulmonary dysplasia (25), and intense extracellular matrix (ECM) deposition (26).

It is imperative that we move towards large, well-powered and designed, pathology-targeted, randomized controlled trials to better define the role of different FiO_2 and PaO_2 targets on relevant clinical outcomes. The findings of such trials may then be further analyzed in individual-data meta-analyses to investigate additional effects and secondary outcomes.

As pointed out by Aggarwal *et al.* (14), training physicians to better control oxygen levels with more rigorous titration

is feasible, but it will be a slow process. Nevertheless, the recent study by the same authors (3) is a valiant effort to move forward and overcome clinicians' inertia to changing FiO_2 toward lower levels. This change in practice may affect the outcomes of ARDS patients.

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Footnote

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