Editorial

Between hypoxia or hyperoxia: not perfect but more physiologic

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The main goal of mechanical ventilation in patients with acute distress respiratory syndrome (ARDS) is to provide an adequate oxygenation, and respiratory support and supplemental oxygen are necessary measures in most patients (1). It has been previously reported that, among ARDS survivors, the prolonged exposure to even moderate hypoxemia can determine neurological complications and cognitive dysfunction (2). Supplemental oxygen is also part of the acute management of different critical conditions including cardiac arrest and circulatory shock, in order to compensate the imbalance between oxygen supply and requirements (3).

However, aggressive treatment of hypoxia might lead to patients' exposure to high levels of fraction of inspired oxygen (FIO_2), even higher than the values strictly necessary to maintain physiologic values of PaO_2, sometimes for a prolonged time. The effects of ventilation with high FIO_2 might have a detrimental effect on patients' outcome mediated by several pathophysiological mechanisms (4). Hyperoxia may produce mitochondrial damage, lipid peroxidation of neuronal cells and an increase in reactive oxygen species (ROS) from high tissue oxygen tension and induce lung injury (5). Hyperoxia following prolonged breathing of very high FIO_2 (especially above 0.90) has shown to be able to cause a direct damage to pulmonary capillary endothelium with consequent altered permeability pulmonary oedema and may exacerbate alveolar inflammation causing severe hyperoxic acute lung injury (HALI), whose severity is directly proportional to PaO_2, with a peak above 450 mmHg (6). Moreover, hyperoxic reperfusion may cause hippocampal neuronal death and lead to neurological complications and brain injury (7,8). In a large multicentre observational study based on administrative data, Kilgannon *et al.* explored the effect of post resuscitation hyperoxia in a large cohort of cardiac arrest and they found that hyperoxia (defined as PaO_2 ≥300 mmHg) were independently associated in-hospital mortality, with an increase of the 24% in risk of death each 100 mmHg increase of partial pressure of oxygen (PaO_2) (9). Similarly, in a recent randomized trial, Girardis *et al.* assigned critically ill patients to receive oxygen therapy targeting PaO_2 between 70 and 100 mmHg or SpO_2 between 94% and 98% (conservative group) or a liberal strategy allowing PaO_2 values up to 150 mmHg or SpO_2 values between 97% and 100% (10). The authors found that a conservative *versus* liberal oxygen therapy reduced ICU mortality. Although these effects are particularly pronounced during long-term administration, several retrospective studies suggest that even short term hyperoxemia is associated with increased mortality and morbidity, especially in patients after cardiac arrest, stroke, and traumatic brain injury (11).

In ARDS patients, despite controversies and authors suggesting to tolerate lower oxygenation levels, most guidelines suggest a compromise between the risks of hypo- and hyperoxia targeting SpO_2 of 88–95% (12). Of notice, in ARDS patients, oxygenation is strongly influenced by FIO_2, but also recruitment manoeuvres positive end-

expiratory pressure (PEEP) (13). While higher PEEP could theoretically allow a reduction of FIO_2, a randomised trial proposing a strategy prioritising PEEP over FIO_2 increase did not show benefits in outcome (14). In the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) an inverse relationship between FIO_2 and SpO_2 was reported, suggesting that in the current practice clinicians use mainly FIO_2 to treat hypoxemia, while no relationship was found between PEEP levels and the PaO_2/FIO_2 ratio, or FIO_2 (15). Moreover, PEEP higher than that strictly necessary to attain the abovementioned SpO_2 goals in conjunction with aggressive recruitment manoeuvres could expose the patient to hyperoxia and might result in an increased mortality (16). However, in ARDS patients few studies systematically investigated the relationship between hyperoxia and increased mortality.

On this basis, Aggarwal *et al.* present an individual data meta-analysis on 2994 patients enrolled in 10 trials performed by the ARDS Network between 1996 and 2013 (17). Patients received lung protective ventilation with PEEP and FIO_2 titrated to oxygen target of PaO_2 between 55 and 80 mmHg or SpO_2 of 88–95%. The authors defined as "above goal oxygen exposure" when the patients were exposed to FIO_2 above 0.5 despite a PaO_2 above 80 mmHg, estimating excess oxygen exposure the difference between the set FIO_2 and 0.5, cumulating this index during the first 5 days. The authors report that the cumulative effect of oxygen exposure above the defined thresholds was independently associated with mortality, with a dose-response effect. The effect on mortality did not differ among different classes of ARDS severity. The authors should be acknowledged for the attempt to explore in detail the effects of excessive exposure to oxygen and the effort to address the issue of the optimal PaO_2, FIO_2 or SpO_2 targets to attain in ARDS patients. Also, results highlight the clinical message that increasing supplemental oxygen to values above those necessary to maintain an acceptable oxygenation should not be done without considering potential adverse effect, as both hypo- and hyperoxia might be dangerous, which seem to confirm previous evidence in critically ill patients (10,18).

However, this explorative analysis could have limitations. First, the authors calculated oxygen exposure from PaO_2 values from a single daily arterial blood gas (ABG) analysis, therefore transient exposures to hyperoxia could have been missed. Moreover, some patient included in the analysis did not have an ABG during the first 5 days of the study, one third did not had missing information concerning ABG at day 0. The lack of these data might have had an impact on final results. Due to the post-hoc nature of the analysis, the authors had to estimate oxygen exposure with a complex definition relying on several assumptions. This method of calculation only represents a surrogate of the real cumulative effect of the dose and the duration of the insult, which should be assessed as area under the curve of the magnitude and persistence in time of excessive oxygen exposure. Second, while the arbitrary threshold of 80 mmHg seems reasonable and in line with the oxygenation goals of the ARDS network trials, in a sensitivity analysis reported in the online supplement increasing the threshold to 100 mmHg values reduced the statistical significance of the finding. This could be either due to a reduction of the number of exposed patients but could also cast doubts about the robustness of the findings. Finally, some confounding factors might represent further limitations of this study. The patient's data collection extended over a 20-year period, and the therapeutic options, indications and ARDS management might have changed over this period. Indeed, as shown in eFigure 1, cumulative oxygen excess at 5 days increased over years, but apparently in the multivariate analysis the time factor is not taken in consideration. Also, the effect of PEEP on oxygen exposure is significant only in the univariable analysis and not in the multivariable, and PEEP and FIO_2 probably have a complex interaction, difficult to assess in a post-hoc analysis.

In conclusion, we believe that although these limitations, the main message that should be taken from this study is that even in patients with ARDS, oxygen administration should be carefully titrated in order to achieve a value of PaO_2 within a physiologic range using the lowest FIO_2 values possible and considering that not only the magnitude but also the persistence of exposure. A strategy of conservative arterial oxygenation has thus a rational basis but needs further validation with high-quality randomized controlled trials to shed a light on the dark aspects of oxygen management.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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