Introduction

Panwar and colleagues recently reported the results of a prospective multicenter international interventional trial comparing two oxygenation targets in all-comer patients receiving invasive mechanical ventilation in ICU, namely a conservative (SpO2 88–92%) versus a liberal target (≥ 96%), by accommodating FIO2 (1). The rationale behind this was that no previous trial was done to compare different oxygenation goals in mechanically ventilated patients. Even though oxygen therapy is frequently used in the critical care setting, its goals are not well defined. The primary outcome was the area under curve of transcutaneous oxygen saturation (SpO2). They included 104 patients in both groups and found that the primary end-point was significantly lower in the conservative than in the liberal group. From this result the authors concluded that reaching a conservative oxygenation target is feasible, which will serve for an upcoming large trial testing these two oxygenation levels.

We would like to split the present editorial into three sections. The first is about the pathophysiological rationale of the study. The second deals with the methodology and the results of the trial. The third will discuss its strengths and limitations.

Pathophysiological rationale

Two basic physiologic tenets are the background of this study, namely oxygen transport and oxy-hemoglobin dissociation curve. Blood oxygen transport to the tissues (TaO2) is equal to cardiac output (L/min) × arterial content (CaO2 in mL/100 mL). CaO2 is equal to Hemoglobin concentration (G/L) × 1.34 mL/mL × SaO2 (%) + 0.0031 (°/mmHg) × PaO2 (mmHg). The oxy-hemoglobin dissociation curve displays the relationship of oxygen arterial saturation (SaO2) to PaO2. It is not linear throughout and two parts can be seen. Below PaO2 55 mmHg/SaO2 90% the relationship is linear with a deep slope. Above this threshold it is curvilinear and large changes in PaO2 are associated with small changes in SaO2. That means that from 95% to 100% SaO2 the magnitude of PaO2 change may widely range between 100 and 600 mmHg. Furthermore, PaCO2 levels, blood pH and temperature are well known factors that shift the oxy-hemoglobin dissociation curve and these are frequently abnormal in the critical care setting. It is therefore complicated to hypothesize for a given patient the relationship between PaO2 and SaO2.

Oxygen therapy should balance risks and benefits of permissive hypoxemia and hyperoxemia due to supra therapeutic oxygen administration. The issues are first the threshold of oxygenation that should indicate the oxygenation supplementation and then the target oxygenation window, within which oxygen administration should be titrated further.

The risks of hypoxemia are cell oxygen deprivation in tissues like brain and heart. It should be mentioned that hypoxemia has a vasodilator effect in some regional circulations like kidney (2) but a vasoconstrictor effect in the pulmonary circulation.

Permissive hypoxemia can worsen an ongoing tissue hypoxia, due for example to a circulatory failure. Indeed, for SaO2 less than 90%, small decrease in PaO2 leads to
major fall in SaO₂ and therefore in CaO₂ and hence TaO₂. Acute and chronic hypoxemia is associated with multiple pathophysiological pathways activation (hypoxic pulmonary vasoconstriction, activation of HIF1, ET-1, NFκB and arachidonic acid pathway) (3). Nevertheless, the threshold of life-threatening hypoxemia is not well defined and a value of PaO₂ of 55 mmHg is usually accepted. Interestingly, this value indicates long-term oxygen therapy in COPD patients.

On the other side of the spectrum, hyperoxemia can be associated with oxidative stress, ischemia-reperfusion lesions, absorption atelectasis (4). In patients with acute myocardial infarction, but without hypoxemia, 8 L/min pure oxygen supplementation was associated with larger infarct size as compared to no oxygen supplementation (5). In patients who had recovered from cardiac arrest restrictive oxygen use may be associated with some benefits to patient outcome (6). Furthermore, hyperoxemia might be harmful for two other reasons, which are clinically relevant.

First, hyperoxemia may result from the deliberate use of potentially harmful ventilator settings like higher tidal volume or higher positive end expiratory pressure.

Second, as previously mentioned, at high PaO₂ level marked drop in PaO₂ can be heightened because, due to the shape of the oxy-hemoglobin dissociation curve, SaO₂ will slightly change. So, important serious events altering gas exchange can be occurring without immediate warning to the clinician. Finally, previous attempts to supra maximize oxygen transport were associated with no (7) or even harmful (8) effect on patient outcome.

Given the inclusion criteria selected by the authors, the study investigated the impact of low or high oxygenation targets in patients under invasive mechanical ventilation with or without hypoxemia at the baseline. That means that the toxicity of lower or higher levels of oxygenation on one hand and the oxygen needs on the other hand are similar in any ICU patients.

The relationship of hypoxemia to death is well documented in ARDS patients (9). That does not mean that reverting hypoxemia would increase survival. The opposite was even true in the ARMA trial (10) where the lower tidal volume group had the worst hypoxemia but the highest survival. Indeed the paradigm in ARDS shifted from oxygenation target to prevention of ventilator-induced lung injury (11). The ARDSnet performed several high-quality trials by using oxygenation target, which was in the range of the conservative arm of present study (10). This target has been used in other large trials on ARDS by investigators not affiliated to the ARDSnet (12-14). In a recent trial on patients with acute hypoxemic respiratory failure and breathing spontaneously high-flow oxygen administered through nasal cannula was compared to oxygen delivered through a face mask and the oxygenation target was SpO₂ 92% to titrate the rate of oxygen delivery in both groups (15). This same threshold was used in a trial on ventilator strategies done in the theatre in patients with normal lungs (16). To date, the BTS guidelines for emergency use of oxygen recommend the 94–98% SpO₂ window except for COPD patients (88–92%) (17), despite a low level of evidence.

Finally, two methodological issues are worth noting and are relevant to the present study. First, the accuracy of SpO₂ device to reflect SaO₂ in ICU patients is not so clear. In a single center study, very large variations between them were found (18). Second, in the perspective of a multicenter large trial the consistency across the blood gas analyzers should be checked.

Methodology and results of present study

In the study by Panwar et al., concerning 103 patients, area under the curve (AUC) for SpO₂, the primary end-point, averaged 93.4% (95% CI: 92.9–93.9%) and 97% (96.5–97.5%) in the conservative and liberal group, respectively (P=0.0001). The mean AUC for PaO₂ was 70 [68–73] mmHg in the conservative arm and 92 [89–96] mmHg in the liberal arm. Furthermore, mean AUC for FiO₂ was lower in the conservative group [0.26 (0.25–0.28)] than in the liberal group [0.36 (0.34–0.39)]. In the conservative group, 14% of time were spent off the target versus 3% in the liberal group (P<0.001). Episodes of arterial desaturation (SpO₂ <86% for more than 5 minutes) were more frequent in the conservative group [1 [0–5] vs. 0 [0–0], P<0.001]. On the other hand, liberal group was exposed more frequently to hyperoxemia (defined as a SpO₂ >98% with FiO₂ >21%), with 22% of the SpO₂ readings meeting this criterion versus 4% (P<0.001). No significant difference in organ dysfunction or mortality was found between the two groups. In the predefined subgroup of hypoxic patients (defined as a PaO₂/FiO₂ <300 mmHg at the time of inclusion), no differences in terms of survival or ventilator support duration were observed between the two strategies.

Discussion of the results and strengths and limitations of the study

This is indeed the first study to investigate two oxygenation
goals in critically ill patients receiving invasive mechanical ventilation.

The conservative strategy was most of the time successfully applied and no excess of morbi-mortality was reported. It supports larger RCT. Higher incidence of arterial desaturation was observed as expected. Jubran et al. previously found that only SpO₂ greater than or equal to 92% (or 95% for black patients) could guarantee PaO₂ greater than 60 mmHg (19). At the same time, the conservative goal was more difficult to reach. This reflects the use of relatively low FiO₂ in this study (despite the presence of at least 20% of patients with ARDS) and one can assume patient with normal lung function exhibits a «normal» SpO₂ when exposed to FiO₂ close to 0.21. It should be noted that almost 50% more arterial blood gases were performed in this group (P=0.04). This may reflect the loss of accuracy of SpO₂ at low values or the concern of clinicians facing low SpO₂.

The liberal group was exposed to SpO₂ greater than or equal to 96%. In terms of either mean SpO₂, PaO₂ or SaO₂ patients in the «liberal» group were within «normal» physiological values for healthy individuals. However, such levels are not recommended for patients with COPD or chronic respiratory failure and could lead to more harm in this population. Interestingly, there were twice more COPD patients in the conservative group (21% vs. 10%).

Hyperoxemia was defined as SpO₂ value of 99% or 100% and henceforth was part of the liberal target. In terms of PaO₂, patients in the liberal group experienced PaO₂ greater than 120 mmHg at 13% of the time points (vs. 3%, P<0.001). It should be noted that no upper alarm is set, which might explain a bigger incidence of hyperoxemia in the liberal arm.

Intermittent hypoxemia, as in the sleep apnea syndrome, occurs at PaO₂ levels observed in the conservative arm. Seven-percent of the time points were with a PaO₂ less than 55 mmHg in the conservative group (versus 1% in the liberal group, P<0.001). Therefore, some patients in the conservative group might have experienced uncontrolled transient hypoxemia, for which chronic effects are known to be detrimental. These negative effects though preferred in case of ARDS over harmful effects of aggressive therapy as discussed above, might have a lower benefits-to-risk balance in other clinical situations.

On the other hand, hyperoxemia is not desired to avoid the potential risk of oxidative stress, notably. Most of the animal studies and the rare human studies reporting these risks were realized with supratherapeutic FiO₂ levels. Recent report of the Hyper2S study done in patients with septic shock demonstrated harmful effect in the hyperoxemia group (P Asfar et al. unpublished results). Patients in this group were exposed to a FiO₂ of 1 during one day. This translates for healthy human to a PaO₂ of at least 400 mmHg. The authors of the present article did not report such PaO₂.

Despite significant results in terms of mean AUC for SpO₂, SaO₂ and PaO₂, there was a large overlap between the two groups, which make results harder to analyze. As specified in the supplementary materials, the conservative group had in fact two targets: (I) SpO₂ 90–92% for FiO₂ <50%; and (II) SpO₂ 88–90% for FiO₂ ≥50%. This could explain the absence of clear difference between patients. It also highlights the variability in the measure of the SpO₂, which might be an argument to SpO₂-based oxygen delivery.

The relatively large inclusion criteria are both strength and a limitation of this study. The heterogeneity of patients reflects the “real life” patients. However, as stressed above, some specific populations (hypoxemic patients, COPD patients, patients with acute circulatory failure) might need a specific target.

Another limitation of the study is the large number of patients (69 pts for 357 pts screened) excluded due to treating physician lacking equipoise. Such an exclusion rate is worrisome and may have offset the advantage of large inclusion criteria. It also might reflect the fear of the clinicians to expose COPD patients to important amount of O₂ or expose healthy individuals to hypoxemia.

The possibility to alter the specified target by the treating physician reflects the bedside practice but also may blunt the effects of the studied targets.

Conclusions

The upcoming large RCT will probably answer most of the questions raised above. However, applying the same oxygenation target to any patient does not seem to go in the direction of a personalized medicine (20). As most of the trials challenging physiological targets (transfusion thresholds, mean arterial pressure goal), we might once again rediscover that «conservative» or «restrictive» management are not so easy to reach and, most of all, that one size does not fit all.

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Footnote

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