Editorial

Conservative versus liberal oxygenation targets for mechanically ventilated patients—a pilot multicenter randomized controlled trial

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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 (SpO_2 88–92%) versus a liberal target (≥96%), by accommodating FIO_2 (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 (SpO_2). 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 (TaO_2) is equal to cardiac output (L/min) × arterial content (CaO_2 in mL/100 mL). CaO_2 is equal to Hemoglobin concentration (G/L) ×1.34 mL/mL × SaO_2 (%) +0.0031 (/mmHg) × PaO_2 (mmHg). The oxy-hemoglobin dissociation curve displays the relationship of oxygen arterial saturation (SaO_2) to PaO_2. It is not linear throughout and two parts can be seen. Below PaO_2 55 mmHg/SaO_2 90% the relationship is linear with a deep slope. Above this threshold it is curvilinear and large changes in PaO_2 are associated with small changes in SaO_2. That means that from 95% to 100% SaO_2 the magnitude of PaO_2 change may widely range between 100 and 600 mmHg. Furthermore, $PaCO_2$ 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 PaO_2 and SaO_2.

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 SaO_2 less than 90%, small decrease in PaO_2 leads to

major fall in SaO_2 and therefore in CaO_2 and hence TaO_2. 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 PaO_2 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 PaO_2 level marked drop in PaO_2 can be heightened because, due to the shape of the oxy-hemoglobin dissociation curve, SaO_2 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 SpO_2 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% SpO_2 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 SpO_2 device to reflect SaO_2 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 SpO_2, 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 PaO_2 was 70 [68–73] mmHg in the conservative arm and 92 [89–96] mmHg in the liberal arm. Furthermore, mean AUC for FiO_2 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 (SpO_2 <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 SpO_2 >98% with FiO_2 >21%), with 22% of the SpO_2 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 hypoxemic patients (defined as a PaO_2/FiO_2 <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 SpO_2 greater than or equal to 92% (or 95% for black patients) could guarantee PaO_2 greater than 60 mmHg (19). At the same time, the conservative goal was more difficult to reach. This reflects the use of relatively low FIO_2 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» SpO_2 when exposed to FiO_2 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 SpO_2 at low values or the concern of clinicians facing low SpO_2.

The liberal group was exposed to SpO_2 greater than or equal to 96%. In terms of either mean SpO_2, PaO_2 or SaO_2 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 SpO_2 value of 99% or 100% and henceforth was part of the liberal target. In terms of PaO_2, patients in the liberal group experienced PaO_2 greater than 120 mmHg at 13% of the time points (*vs.* 3%, P<0.001). It should be noted that no upper alarm for SpO_2 was set, which might explain a bigger incidence of hyperoxemia in the liberal arm.

Intermittent hypoxemia, as in the sleep apnea syndrome, occurs at PaO_2 levels observed in the conservative arm. Seven-percent of the time points were with a PaO_2 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 FiO_2 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 FiO_2 of 1 during one day. This translates for healthy human to a PaO_2 of at least 400 mmHg. The authors of the present article did not report such PaO_2.

Despite significant results in terms of mean AUC for SpO_2, SaO_2 and PaO_2, 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) SpO_2 90–92% for FiO_2 <50%; and (II) SpO_2 88–90% for FiO_2 ≥50%. This could explain the absence of clear difference between patients. It also highlights the variability in the measure of the SpO_2, which might be an argument to SpO_2-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 O_2 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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