Editorial

Permissive hypoxemia/conservative oxygenation strategy: Dr. Jekyll or Mr. Hyde?

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Oxygen is one of the essentials required for sustaining life, which plays an important role in human medical history. It has become a routine therapy for critically ill patients, and the assessment and administration of oxygen in the ICU gained more and more attention (1,2). Both hypoxia and hyperoxia is related to adverse outcome. de Jonge *et al*. demonstrated that there was a U-shaped relationship between PaO_2 and in-hospital mortality, the lowest of the mortality being at PaO_2 values of 110–150 mmHg; mortality sharply increased both at PaO_2 values <67 and >225 mmHg (3). Nowadays, the "double-edged sword" character of oxygen is well established. On one hand, the hypoxia result in the imbalance between O_2 supply and requirements, which could induce tissue hypoxia and cell death. On the other hand, the presence of hyperoxia enhances reactive oxygen species (ROS) and oxidative stress, which cause alveolar and cell damage. The benefit/harm ratio of oxygen therapy is determined by the O_2 dose, exposure duration, and underlying diseases. To reduce the potential risks of hyperoxia, a lower oxygenation targets may be acceptable in critically ill patients. A tolerable low SaO_2 also termed as permissive hypoxemia/conservative oxygenation strategy. Generally, the permissive hypoxemia strategy aims for an SaO_2 between approximately 85% and 95%, which always use in the ARDS patients and preterm infants (4,5).

Recently, Panwar *et al*. present an intriguing pilot randomized, controlled, unblinded, international multicenter study in which they compared a conservative oxygenation strategy (aimed target SpO_2 88–92%) to a traditional, liberal strategy (aimed target SpO_2 96%) in the *Am J Respir Crit Care Med* (6). There were no significant between-group differences in any measures of new organ dysfunction, or ICU 90-day mortality. The study was well conducted with excellent adherence to study protocol and successful intervention. The authors concluded conservative oxygenation strategy is a feasible alternative to the usual liberal oxygenation strategy, while being effective in reducing exposure to hyperoxia.

However, some important points merit discussion. First, the concept of "permissive hypoxemia" is similar to the "permissive hypercapnia" or "permissive impaired peripheral perfusion" (4,7). To some extent, the adaption of cellular and organ may occur during hypoxemia that facilitates survival without increased harm. It has been acceptable maintaining normal physiology status could result in further injury compared to keep the permissive impaired physiological status in critically ill patients. Here, we stress the concept of permissive hypoxemia reflect the careful balance between the target SaO_2 and the ventilator toxicity required to achieve a higher SaO_2, not just a specific SaO_2 goal. Furthermore, the conservative oxygenation strategy/permissive hypoxemia therapy should be used in some selected patients who are with a high risk of hyperoxia, but not for all patients. Studies have shown hyperoxia is associated to poor outcome in the post-cardiac arrest, traumatic brain injury, and ischemic stroke patients. Permissive hypoxemia always works as a lung-protective strategy that aims to minimize the detrimental effects of the usual ventilatory support in ICU (8). Second, the purpose of permissive hypoxemia deserves clarification. Apparently, the permissive hypoxemia is used to avoid the harm of hyperoxia in clinical practice. So, the injury of hyperoxia should be well defined according to different

patients. Study demonstrated the severe hyperoxia (PaO_2 >300 mmHg) but not moderate hyperoxia (101–299 mmHg) is related to bad outcome, and moderate hyperoxia (101–299 mmHg) was associated with improved organ function at 24 h in the cardiac arrest (9). Interestingly, there was no patients with severe hyperoxia (PaO_2 >300 mmHg) in the usual liberal oxygenation strategy group in Panwar' study, and the patients with PaO_2 >150 mmHg also was rare. In other words, the usual liberal oxygenation strategy might be enough to avoid a toxic dose of oxygen therapy. Most clinicians believed mild hyperoxia would provide a reservation of oxygen, and fear the potential risk of hypoxemia in the critically condition. The adverse and benefit effects of exposure to mild hyperoxia need further research to investigate. Third, permissive hypoxemia also could increase pulmonary artery pressure (through hypoxic pulmonary vasoconstriction) and subsequently cause right ventricular dysfunction (10,11). Therefore, it would be a dilemma to implement the permissive hypoxemia in the ARDS patients with acute cor pulmonale. We suggest the right heart function should be monitored and assessed in the implementation of permissive hypoxemia.

Another concern is the definition of hyperoxia in Panwar' study. Both arterial hyperoxia and high fraction of inspired O_2 is related to hyperoxia. The most commonly used threshold to define hyperoxia was PaO_2 >300 mmHg (12), which is related to poor outcome. On the other hand, the lung tissue is continuously and directly exposed to oxygen, so inspire high fraction of O_2 might also result in lung damage. "Hyperoxic acute lung injury (HALI)" was used to describe the pulmonary-specific toxic effects of O_2. The severity of HALI is directly proportional both to the PO_2 (particularly above 450 mmHg, or a FiO_2 of 0.6) and the duration of exposure (13). Therefore, the target of permissive hypoxemia is not only a low SaO_2 but also a low FiO_2. The arterial hyperoxia must result from high FiO_2, but high FiO_2 could not guarantee arterial hyperoxia. Furthermore, the high FiO_2 is required to maintain the acceptable SaO_2 in the severe ARDS patients after the optimization of mechanical ventilation, and permissive hypoxemia might be more relevant in this condition.

Another big problem of implementation permissive hypoxemia is how to avoid tissue hypoxia and keep the balance between DO_2 and VO_2. Systemic oxygen delivery (DO_2) is the product of the arterial oxygen content and cardiac output, and the SaO_2 would play a significant effect on arterial oxygen content before SaO_2 reach to 100%. So, the relationship between DO_2 and VO_2 should be carefully evaluated during the implementation of permissive hypoxemia. The presence of normal central venous oxygen saturation (>70%), central venous-to-arterial CO_2 difference (<6 mmHg), lactate (<2 mmol/L) and central venous-to-arterial CO_2 difference/arterial-central venous O_2 difference ratio (<1.23) indicate the adequacy of DO_2 (14). The dynamic assessment of these related parameters would be useful to adjust the target of SaO_2 during permissive hypoxemia. In addition, the manipulate sedation, hemoglobin and cardiac output is also helpful to guarantee global oxygen delivery during the conservative oxygenation strategy (15).

Generally speaking, oxygen therapy should be a goal-directed, and early monitoring of both pulse oximetry and arterial blood gases is advised. Permissive hypoxia is one part of the oxygen administration strategy. Although the Panwar' study supported the feasibility of permissive hypoxia, but the evidence still is lacking in terms of the efficacy (16). Recently, the UK and Australian Benefits of Oxygen Saturation Targeting (BOOST) II trials showed an oxygen saturation target of 85% to 89%, rather than 91% to 95%, may increase the risk for death or disability at 2 years corrected age in infants born before age 28 weeks (17). The potential harm of hypoxia should be careful evaluated based on the pathological and physiological conditions, and it should be reminded that the benefit of permissive hypoxia is derived from the reduction of hyperoxia injury.

In conclusion, clinical evidence supporting permissive hypoxemia is not currently available and it will be important to carefully evaluate the risks and benefits of permissive hypoxia before proceeding to efficacy and effectiveness trials. Choosing the right therapeutic target and right patients is the key to make the permissive hypoxia strategy become Dr. Jekyll but not Mr. Hyde. So, we suggest future studies of permissive hypoxia should focus on the severe ARDS patients with high FiO_2 but not in critically ill patients with regular mechanical ventilation.

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