Review Article

Relationship between hyperoxemia and ventilator associated pneumonia

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Contributions: (I) Conception and design: K Jaffal, S Six, S Nseir; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: K Jaffal, S Six; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Previous studies suggest a relationship between hyperoxemia and ventilator-associated pneumonia (VAP). Hyperoxemia is responsible for denitrogenation phenomena, and inhibition of surfactant production, promoting atelectasis in mechanically ventilated patients. Further, hyperoxemia impairs the efficacy of alveolar macrophages to migrate, phagocyte and kill bacteria. Oxygen can also cause pulmonary-specific toxic effect called hyperoxic acute lung injury leading to longer duration of mechanical ventilation. All these hyperoxic effects are well-known risk factors for VAP. A recent retrospective large single center study identified hyperoxemia as an independent risk factor for VAP. However, two recent randomized controlled trials evaluated the impact of conservative oxygen strategy versus a liberal strategy, but did not confirm the role of hyperoxemia in lower respiratory tract infection occurrence. In this review, we discuss animal and human studies suggesting a relationship between these two common conditions in mechanically ventilated patients and potential interventions that should be evaluated. Further large prospective studies in carefully selected groups of patients are required to confirm the potential role of hyperoxemia in VAP pathogenesis and to evaluate the impact of a conservative oxygen strategy *vs.* a conventional strategy on the incidence of VAP.

Keywords: Hyperoxemia; ventilator-associated pneumonia (VAP); infection; intensive care unit (ICU)

Submitted Oct 03, 2017. Accepted for publication Oct 10, 2017.
doi: 10.21037/atm.2017.10.15
View this article at: http://dx.doi.org/10.21037/atm.2017.10.15

Introduction

High concentrations of oxygen are routinely used during the supportive care in critically ill patients (1,2). Liberal oxygen therapy is supposed to prevent hypoxia and improve oxygen supply to the different affected organs. However, oxygen toxicity has recently raised concern regarding the liberal use of oxygen. Because of its unique properties as a final electron receptor, O_2 allows high rate of adenosine triphosphate (ATP) synthesis in the respiratory chain pathway, making molecular O_2 vital for mammalian cells. However, O_2 is among the strongest oxidizing agents due to its high oxidizing chemical property that can damage all biological molecules (3,4).

Hyperoxemia commonly occurs because clinicians maintain super-normal PaO_2 to provide a buffer or margin of safety in case of acute desaturation, forgetting that the O_2-carrying capacity of plasma is minor (0.003 mL/dL/mm Hg of PaO_2), as compared with hemoglobin (1.39 mL/g/dL). The main end point should be tissue oxygenation that reflects the balance between oxygen delivery and tissue consumption. In most of cases hyperoxemia does not lead to adjustment of ventilator settings if inspired oxygen fraction (FiO_2) <0.40, level generally considered safe by clinicians (4,5).

Although existing data remain conflicting regarding the risk related to hyperoxemia in critical care, results from the

latest clinical studies suggest that hyperoxemia is probably associated with worse outcomes in some critically ill patients (6,7). Potential reasons for these conflicting results are significant heterogeneity between the studies regarding hyperoxemia definition, time of assessment, cutoffs, timing and duration of hyperoxemia. Two meta-analyses suggest that hyperoxemia is associated with increased mortality in different populations of critically ill patients (8,9), including post-cardiac arrest [OR =1.42 (1.04–1.92), I^2=68%], stroke [OR =1.23 (1.06–1.43), I^2=0%], and traumatic brain injury [OR =1.41 (1.03–1.94), I^2=65%].

Previous studies suggested a relationship between hyperoxemia and ventilator-associated pneumonia (VAP). VAP is the most common intensive care unit (ICU)-acquired infection (10) and is associated with high mortality, duration of mechanical ventilation, and cost (11). Better understanding of pathophysiology and risk factors for VAP is a key issue in improving preventive strategies. The aim of this narrative review is to discuss animal and clinical studies regarding the possible relationship between hyperoxemia and VAP.

Experimental studies

Oxygen toxicity is mainly related to the formation of reactive oxygen species (ROS), especially during hypoxia/re-oxygenation and long exposure to oxygen (12-14). The enhanced rate of ROS formation is directly related to the O_2 partial pressure. ROS have both toxic and vital potential for host defense and as signaling molecules (15,16).

It has been well-established for more than a century that pulmonary O_2 toxicity may cause severe pulmonary inflammation leading to hemorrhagic pulmonary edema and fibrosis (17-20). High level of FiO_2 is responsible for denitrogenation phenomena and inhibition of surfactant production promoting expiratory collapse and atelectasis (21-23). Adsorption atelectasis occurs within few minutes after pure O_2 breathing (23-25). In mechanically ventilated patients, atelectasis seriously impairs cough reflex and mucus clearance resulting in abundant secretions in the lower airways and higher risk for VAP (26,27).

Prolonged hyperoxia impairs the efficacy of alveolar macrophages to migrate, phagocyte and kill bacteria (28-31), resulting in decreased bacterial clearance. Hyperoxemia markedly increased the lethality of both *Legionella pneumophila* and *Pseudomonas aeruginosa* in a mouse models of pneumonia (32,33). No mortality was observed in mice exposed to either bacterial inoculation or hyperoxemia alone, but this combination lead to loss of barrier integrity and systemic dissemination of bacteria (32). This increased mortality in animals occurred even at 40% to 65% of FiO_2 (31,34,35), levels generally considered safe by clinicians (36).

Additionally, O_2 can cause pulmonary-specific toxic effect called hyperemic acute lung injury (HALI) (13), initially described by Smith *et al.* in 1899 (37,38). Hyaline membrane formation, pulmonary arteriole thickening, and alteration in the ventilation/perfusion fraction are the main mechanisms described (13). The pathophysiology of HALI is similar to that of acute respiratory distress syndrome (ARDS).

All the above-discussed side effects of hyperoxemia, including pulmonary inflammation, atelectasis, and impaired bacteria clearance are well-known risk factors for VAP (39-43). The impact of these consequences of hyperoxemia on VAP occurrence is presented in *Figure 1*.

Clinical studies

Observational studies reported that hyperoxemia was present in more than 50% of mechanically ventilated patients during the first 24 h after ICU admission (1,44). Although several observational studies suggested an association between hyperoxemia and poor hospital outcomes, recent meta-analyses were inconclusive due to the high data heterogeneity (4,8). However, recent randomized controlled trials also suggest that hyperoxemia might be harmful in critically ill patients.

Girardis and colleagues performed a large randomized controlled trial to evaluate the impact of conservative (PaO_2 between 70 and 100 mmHg, or SpO_2 between 94% and 98%) versus conventional oxygen therapy (PaO_2 values up to 150 mmHg, or SpO_2 values between 97% and 100%) on mortality in ICU patients (6). ICU-mortality rate was significantly lower in the conservative compared with the conventional group [11.6% *vs.* 20.2%, absolute risk reduction 0.086 (95% CI: 0.017–0.150)]. Although the rate of new bloodstream infections was significantly lower in the conservative compared with the conventional group [absolute risk reduction 0.005 (95% CI: 0.000–0.009)], the rate of nosocomial respiratory infections was similar in the two groups. However, several confounders could have influenced the results reported by Girardis and colleagues regarding the absence of significant impact of hyperoxemia on respiratory infection rate. First, the authors used CDC criteria to define respiratory infections. These criteria are not specific, and the authors did not clearly differentiate ventilator-associated tracheobronchitis (VAT) from VAP. Although these infections are classified as respiratory

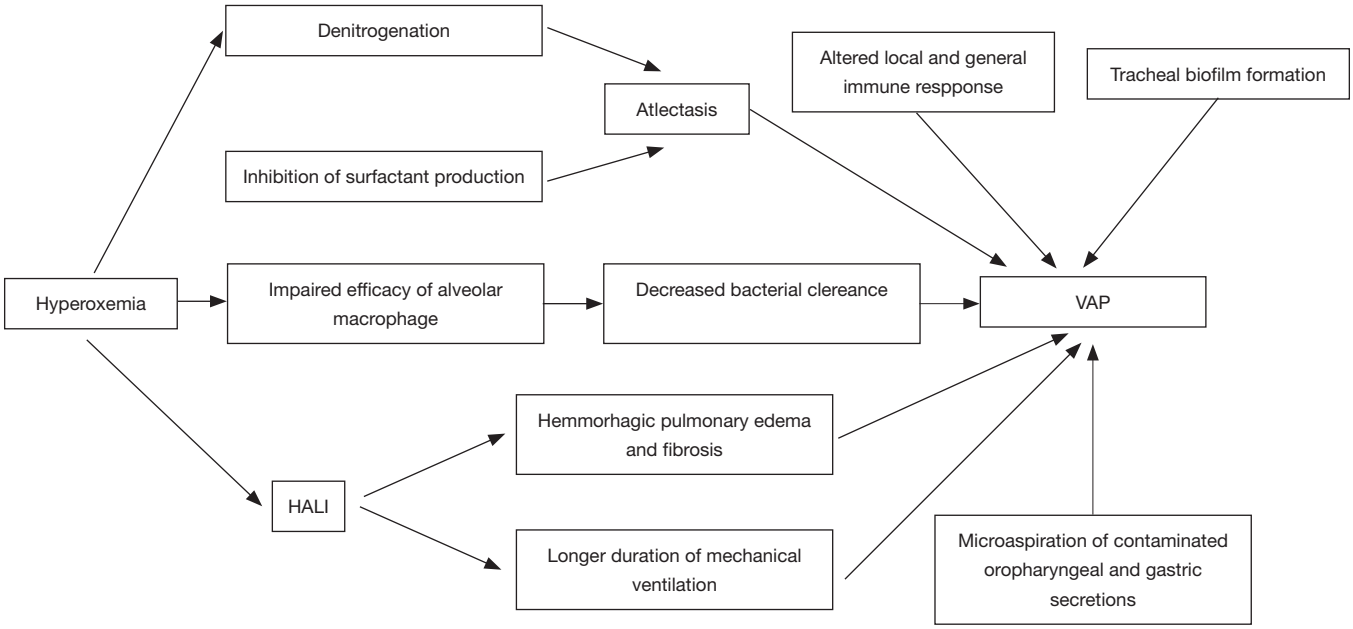

Figure 1 Relationship between hyperoxemia and VAP. VAP, ventilator-associated pneumonia; HALI, hyperoxic acute lung injury.

infections by CDC criteria, their impact on mortality is clearly different. A recent large observational multinational study showed that VAP, but not VAT, was associated with significantly higher mortality rate, compared with patients with no lower respiratory tract infections (45). Second, no information is given on the methods used to obtain the microbiological confirmation in patients with respiratory infections. It is well known that the use of quantitative methods substantially improves the specificity of VAP diagnosis. Third, the exclusion of immunosuppressed, ARDS, and COPD patients might have influenced their results, as these patients are at higher risk for VAP. Fourth, no information is give on incidence density of VAT and VAP (number of infections per 1,000 mechanical ventilation days) in study groups.

Recently, Asfar and colleagues performed a two-by-two factorial, randomized controlled clinical trial (HYPERS2S) to determine the impact of hyperoxemia and fluid resuscitation with hypertonic saline solution in patients with septic shock, versus normoxemia and isotonic saline on mortality (7). The trial was stopped early for safety reasons, and the authors concluded that in patients with septic shock setting FiO_2 to 1.0 to induce hyperoxemia might increase the risk of mortality, and hypertonic saline did not improve survival. Interestingly, the percentage of patients with atelectasis doubled in patients with hyperoxemia compared with those with normoxemia (12% *vs.* 6%, P=0.04). However, no significant difference was found in nosocomial pneumonia rate between the two groups (15% *vs.* 14%, P=0.78). ICU-acquired pneumonia was not the primary outcome of this trial. Moreover, several other factors preclude any valuable conclusion on the relationship between hyperoxemia and ICU-acquired pneumonia (46). First, no clear definition is given for ICU-acquired pneumonia, and if the same definition of ICU-acquired pneumonia was used in the different participating ICUs (n=22) is not reported. Second, the density rate of ICU-acquired pneumonia is not provided. Third, whether quantitative microbiological confirmation was required in all patients is unknown. Although the incidence of ICU-acquired pneumonia is in line with rates reported by French ICUs, applying different diagnostic criteria to the same patient population can result in wide variation in the incidence of nosocomial pneumonia. A recent study showed that the incidence of VAP ranged from 4% to 42% when using the six published sets of criteria in the same cohort of patients (47). Further, it is well known that the use of quantitative methods substantially improves the specificity of VAP diagnosis.

Rachmale and colleagues (48) prospectively evaluated the electronic medical record of 289 ICU patients with acute lung injury to assess excessive oxygen exposure and its effect

on pulmonary outcomes. Excessive FiO_2 was defined as FiO_2 >0.5. Results showed that 74% of the included patients were exposed to hyperoxemia. A correlation between prolonged FiO_2 exposure and worsening of oxygenation index in 48 hours, as well as an association between hyperoxemia and longer duration of mechanical ventilation and ICU stay were demonstrated (48). Another recent large multicenter cohort study found severe hyperoxemia to be associated with fewer ventilator-free days and higher mortality (4). Longer duration of mechanical ventilation is a well-known a factor risk for VAP (49).

Our group performed a large single center cohort study to determine the relationship between hyperoxemia and VAP (50). VAP was diagnosed using clinical, radiological and quantitative microbiological data in 28% (128 out of 503) of study patients. Multivariate analysis identified number of days spent with hyperoxemia [OR =1.1, 95% CI: (1.04–1.2) per day, P=0.004], simplified acute physiology score (SAPS) II [OR =1.01, 95% CI: (1.002–1.024) per point, P<0.05], red blood cell transfusion (OR =1.8, 95% CI: 1.2–2.7, P=0.01), and proton pomp inhibitor use (OR =1.9, 95% CI: 1.03–1.2, P<0.05) as independent risk factors for VAP. Other multiple regression models also identified hyperoxemia at ICU admission (OR =1.89, 95% CI: 1.23–2.89, P= 0.004), and percentage of days with hyperoxemia (OR =2.2, 95% CI: 1.08–4.48, P=0.029) as independent risk factors for VAP. However, the study was retrospective, performed in a single center, and the definition used for hyperoxemia (at least one PaO_2 value >120 mmHg per day) could be a matter for debate.

Future research and potential interventions

Conservative O_2 strategy

The results of recent studies highlight the importance of clinical management strategies that prevent hypoxemia while minimizing the incidence of hyperoxemia (51). Even now, nearly 240 years after the discovery of O_2, what constitutes the safe upper limits and duration of FiO_2 remains uncertain. Toxicity rose more rapidly as FiO_2 is increased above 0.6 and also as exposure time is prolonged (4,18,37,38). Available data showed a U-shaped relationship between mortality and arterial PaO_2 (52). Mortality sharply increased at PaO_2 <65 and >225 mmHg (1). Based on these concerns and the fact that optimizing oxygenation targets may improve patients' outcome, oxygen titration should be done. With appropriate safeguards, lower oxygenation targets may be acceptable and possibly beneficial in many critically ill patients.

Conservative oxygen therapy with careful oxygen titration is aimed at the prevention of iatrogenic hyperoxemia while preserving adequate tissue oxygenation. Several studies have now compared so-called conservative oxygen strategies targeting lower PaO_2 or SpO_2 values with conventional oxygen administration and reported no significant differences in terms of organ dysfunction or ICU and 90-day mortality (6,8,9,53). Suzuki *et al.* reported a lower atelectasis score and shorter duration of mechanical ventilation in the conservative oxygen therapy group, as compared with the liberal group (54,55). Also, in the study of Helmerhorst *et al.*, ventilator-free days were greater higher in the conservative oxygen therapy, as compared with liberal oxygen group (4,56). Further, conservative oxygen strategy seems to be safe and feasible (53,54,56).

Permissive hypoxemia

The conservative oxygen strategy has led to the concept of *permissive hypoxemia* (with hemoglobin concentration 9–10 g/dL and normal cardiac index 4.7 L/min/m^2, in order to maintain normal O_2 tissue delivery) in some selected patients with a high risk of hyperoxemia like severe ARDS patients. This oxygen administration strategy works as a lung-protective strategy that aims to minimize the detrimental effects of the usual ventilatory support in the ICU (57). Although studies supported the feasibility of permissive hypoxemia, evidence is still lacking in terms of the efficacy (53,58). 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 (59). No study in adults is yet available.

Automated FiO_2 adjustment

With the use of pulse oximetry and computer technology, several attempts have been made to automate the adjustment of FiO_2, especially in neonatology, because of the frequent and unpredictable change of oxygenation and risks of hyperoxemia in premature babies (60) as well as for titrating the FiO_2 for COPD patients requiring long-term oxygen therapy (61). These systems proved a reduction in oxygen use without inducing hypoxemia compared with conventional adjustments. Last, a recent mode of ventilation

allows full control of both pressure-targeted breaths and the level of FiO_2 in a closed-loop manner (62-64).

Antioxydants supplementation

Antioxidant supplementation has been used to reduce hyperoxemia-compromised host defense by scavenging hyperoxemia-induced excessive intracellular ROS. Treatment of hyperoxemia-exposed macrophages with antioxidants, such as superoxide dismutase can preserve actin cytoskeleton organization and increase the phagocytosis of bacteria (31,65). Hyperoxemia-exposed cells overexpressing antioxidant enzyme manganese superoxide dismutase, have increased phagocytic activity, attenuated ROS-induced damage and reduced bacterial adherence (65,66). In a mice model exposed to hyperoxemia, ascorbic acid supplementation significantly improved bacterial clearance of *P. aeruginosa* (67). Another recent animal study suggests that hyperoxemia increases mortality in mice with *Acinetobacter baumannii* pneumonia, and that procysteine improves survival by increasing the phagocytic activity of alveolar macrophages (68). These findings suggest that supplementation with antioxidants during supportive oxygen therapy may be an effective intervention to attenuate or prevent the development of VAP in critically ill patients. A better understanding of the signaling pathways induced by hyperoxemia may provide valuable insights on its pathogenesis and may help in designing more effective therapeutic approaches.

Conclusions

Animal and clinical studies suggest a link between hyperoxemia and VAP. However, further large prospective studies in carefully selected groups of patients are required to confirm these findings and to evaluate the impact of a conservative oxygen strategy *vs.* a conventional strategy on the incidence of VAP.

Acknowledgements

None.

Footnote

Conflicts of Interest: S Nseir—Medtronic, and MSD (lecture); Ciel Medical, and Bayer (advisory board). The other authors have no conflicts of interest to declare.

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Cite this article as: Jaffal K, Six S, Zerimech F, Nseir S. Relationship between hyperoxemia and ventilator associated pneumonia. Ann Transl Med 2017;5(22):453. doi: 10.21037/atm.2017.10.15

