Correspondence

The unknowns about oxygen therapy in critically ill patients

Rakshit Panwar[1,2]

[1]Intensive Care Unit, John Hunter Hospital, Newcastle, Australia; [2]School of Medicine and Public Health, University of Newcastle, Newcastle, Australia

Correspondence to: Rakshit Panwar. Intensive Care Unit, John Hunter Hospital, Newcastle, Australia. Email: rakshit.panwar@hnehealth.nsw.gov.au.

Submitted Sep 30, 2016. Accepted for publication Oct 12, 2016.
doi: 10.21037/jtd.2016.11.85
View this article at: http://dx.doi.org/10.21037/jtd.2016.11.85

Oxygen is a commonly used drug in healthcare (1). Despite the widespread and age-old use of oxygen therapy in acutely ill patients, there are several unknowns when some of the basic questions pertaining to the use of any drug are asked. On one hand, supra-physiological oxygen levels are often targeted, and achieved, in conventional practice (2-4), despite the lack of high-quality evidence that using supplemental oxygen to achieve the conventional hyperoxic levels has any benefit. Additionally, recent studies have highlighted potential harms associated with hyperoxia (5-7). On the other hand, harms of poor oxygenation and tissue hypoxia are well established. However, the incidence and severity of such harmful effects, the upper and lower oxygenation thresholds at which these harmful effects begin to occur, the inter-individual variability in the physiological response to abnormal oxygen levels, the time-dependent and the dose-dependent characteristics of harmful effects, and their long term safety data remain unclear. Just as the threshold for permissive hypoxemia is not clearly defined (8), the threshold for hyperoxia or hyperoxemia remains unclear too (6,9). Further, not only the oxygenation-related thresholds for potential injury may be different for different patients (10), but they may vary with different stages of a disease in the same patient. It seems inaccurate to extrapolate these threshold levels from the observational studies, where outcomes could be influenced by many recognized or unrecognized confounders. The bottom line is that the current state of knowledge is inadequate to recommend optimal oxygen targets among acutely ill patients. Therefore, it is imperative for the critical care research groups to lay the ground work for conducting well designed trials that can address some of these basic questions about oxygen therapy.

Several strategies have been recently proposed for the management of hypoxemic ICU patients. A strategy of "*precise control of arterial oxygenation*" can avoid significant fluctuations beyond a narrowly defined normoxemic range, and thus avoid potential adverse effects of hyperoxia usually attained in conventional practice (9,10). A strategy of "*conservative oxygenation therapy*" aims to restrict use of supplemental oxygen for the purpose of avoiding hypoxemia (i.e., target SaO_2 ≥90%) (11). A conservative strategy often targets the lower end of the acceptable range for arterial oxygenation levels (i.e., target SaO_2 88–92%) (12). A strategy of "*permissive hypoxemia*" aims to restrict use of supplemental oxygen to achieve even lower oxygenation levels than are currently acceptable (10,13), which may be suited for patients who either have had time to adapt to subacute or sustained hypoxemia or have such severe gas exchange abnormality that the risks of interventions needed to achieve the desired oxygenation level outweigh the benefits of achieving that goal. Last, the strategy of "*individualized oxygen therapy*" is also gaining traction in this era of personalized health care. This strategy likely encompasses the previous three strategies with an aim to manage hypoxemia guided by the clinical response, the best available evidence, anticipated duration that supplemental oxygen may be needed, and the current stage of the disease in a patient. All these strategies need careful and prudent ongoing investigations.

Some clinicians suggest that the conservative oxygen therapy or permissive hypoxemia should only be used in a select group of patients who are at a high risk of hyperoxia, but not for all patients (14). However, it might be premature to assume that hyperoxic injury is unlikely to happen in a particular group of patients before being tested in an experimental setting. A normal lung is certainly no guarantee against hyperoxic injury, which is demonstrated to be directly related to both inspired concentration of oxygen (FiO_2)

and the duration of exposure to excessive FiO_2 (15-17). Progression of the initial lung insult is not uncommon in ICU (18). One-third of the patients developed acute lung injury or ARDS at a median of three days after the ICU admission in a large observational study (19). Existing evidence suggests that a subclinical or a preexisting insult to the lung may change the susceptibility to oxygen-induced lung damage, which may cause or augment the severity of the lung injury (20-24). For these reasons, a broad group of ICU patients who are exposed to supplemental oxygen on a routine basis, while on invasive mechanical ventilation, must be studied in future pragmatic RCTs on different strategies of oxygen therapy. Explanatory trials are also needed to study if different oxygenation strategies have different effects on the clinical outcomes in specific conditions such as elderly, ARDS, traumatic brain injury or stroke, post cardiac arrest syndrome or circulatory shock state.

A major concern often raised with restrictive oxygen therapy is its lowering effect on systemic oxygen delivery (14). However, physiological studies show this effect to be trivial. Given that the systemic oxygen delivery is the product of cardiac output and arterial blood oxygen content (CaO_2), the effect of liberal versus restrictive oxygen therapy on both these factors need to be considered. First, high FiO_2 therapy or hyperoxia is demonstrated to markedly reduce coronary blood flow due to coronary vasoconstriction (25) with variable hemodynamic effects. In awake patients, high FiO_2 therapy showed no significant effects on stroke volume index or cardiac index (26), whereas among anaesthetized patients, increasing FiO_2 reduced cardiac output, and *vice versa* reducing FiO_2 increased cardiac output (27). Second, the sigmoidal shape of the O_2-hemoglobin dissociation curve (28) implies that the likely effect on CaO_2, when PaO_2 is increased from 55 to 150 or 300 mmHg, is trivial. The reason is that beyond a threshold PaO_2 of 55–60 mmHg, large increments in PaO_2 result in little gains in SaO_2 (29), which is a far more important determinant of CaO_2. Indeed in a crossover clinical trial, when a higher SaO_2 target (mean SaO_2 97%; CaO_2 18 mL/dL) was compared to a lower SaO_2 target (mean SaO_2 92%; CaO_2 16.9 mL/dL), there was a difference of just 1.1 mL/dL in the CaO_2 with no significant effect on cardiac output or oxygen consumption (30). Therefore, the overall incremental effect of liberal versus conservative oxygenation on the systemic oxygen delivery is trivial. Nonetheless, interventions targeted at elevating systemic oxygen delivery have consistently failed to improve outcomes among critically ill patients (31,32).

Last, it is well acknowledged that the safety and feasibility of a conservative oxygenation strategy or permissive hypoxemia need careful evaluation (8,12). The notion that either of these strategies might improve clinical outcomes is not without merits. It is plausible that among mechanically ventilated patients, any supplemental FiO_2 over and above 0.21 (i.e., a supra-physiological FiO_2) can cause a local hyperoxic environment that might have a dose-dependent injurious effect on the lung alveoli and surrounding tissues. The injury in pulmonary tissues may evolve or progress with time in presence of ongoing hyperoxia. In addition, a supra-physiological FiO_2 that results in a supra-physiological PaO_2 for an individual patient might cause a dose-dependent and time-dependent hyperoxic tissue injury in other organs, which may result in either new organ dysfunction or delay in recovery. On the other hand, not using sufficient supplemental FiO_2 or targeting SaO_2 or PaO_2 that is lower than currently acceptable limit (permissive hypoxemia) might result in hypoxic tissue injury in other organs. Whether a conservative oxygenation strategy, where the SaO_2 or PaO_2 targets are within the lower end of the currently acceptable range, has better risk-benefit profile than a strategy of permissive hypoxemia remains unclear. We tested the former strategy in a feasibility trial to assess whether we can minimize the use of supplemental FiO_2 in presence of an acceptable SpO_2. The SpO_2 targets in the conservative arm were stratified based on the FiO_2 requirement for the patient. When FiO_2 requirement was <0.50, the SpO_2 targets were 90–92%, whereas when FiO_2 requirement was 0.50, SpO_2 targets were 88–90% (12). Clinicians were allowed to alter these targets if they were concerned about adequacy of systemic oxygen delivery or any hypoxic injury. Despite limitations, our study was the first RCT investigating two oxygenation targets among the mechanically ventilated adult ICU patients, and provides important data that may encourage further investigations on different oxygenation strategies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Response to: He HW, Liu DW. Permissive hypoxemia/conservative oxygenation strategy: Dr. Jekyll or Mr. Hyde? J Thorac Dis 2016;8:748-50.

References

1. Bitterman H. Bench-to-bedside review: oxygen as a drug. Crit Care 2009;13:205.
2. de Jonge E, Peelen L, Keijzers PJ, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care 2008;12:R156.
3. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med 2012;38:91-8.
4. Young PJ, Beasley RW, Capellier G, et al. Oxygenation targets, monitoring in the critically ill: a point prevalence study of clinical practice in Australia and New Zealand. Crit Care Resusc 2015;17:202-7.
5. Stub D, Smith K, Bernard S, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 2015;131:2143-50.
6. Damiani E, Adrario E, Girardis M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care 2014;18:711.
7. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, et al. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and Meta-Regression of Cohort Studies. Crit Care Med 2015;43:1508-19.
8. Gilbert-Kawai ET, Mitchell K, Martin D, et al. Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients. Cochrane Database Syst Rev 2014;(5):CD009931.
9. O'Driscoll BR, Howard LS, Davison AG, et al. BTS guideline for emergency oxygen use in adult patients. Thorax 2008;63:vi1-68.
10. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med 2013;41:423-32.
11. Slutsky AS. Consensus conference on mechanical ventilation--January 28-30, 1993 at Northbrook, Illinois, USA. Part I. European Society of Intensive Care Medicine, the ACCP and the SCCM. Intensive Care Med 1994;20:64-79.
12. Panwar R, Hardie M, Bellomo R, et al. Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. Am J Respir Crit Care Med 2016;193:43-51.
13. Capellier G, Panwar R. Is it time for permissive hypoxaemia in the intensive care unit? Crit Care Resusc 2011;13:139-41.
14. He HW, Liu DW. Permissive hypoxemia/conservative oxygenation strategy: Dr. Jekyll or Mr. Hyde? J Thorac Dis 2016;8:748-50.
15. Crapo JD. Morphologic changes in pulmonary oxygen toxicity. Annu Rev Physiol 1986;48:721-31.
16. Nash G, Blennerhassett JB, Pontoppidan H. Pulmonary lesions associated with oxygen therapy and artifical ventilation. N Engl J Med 1967;276:368-74.
17. Rachmale S, Li G, Wilson G, et al. Practice of excessive F(IO(2)) and effect on pulmonary outcomes in mechanically ventilated patients with acute lung injury. Respir Care 2012;57:1887-93.
18. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002;287:345-55.
19. Brun-Buisson C, Minelli C, Bertolini G, et al. Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE study. Intensive Care Med 2004;30:51-61.
20. Aggarwal NR, D'Alessio FR, Tsushima K, et al. Moderate oxygen augments lipopolysaccharide-induced lung injury in mice. Am J Physiol Lung Cell Mol Physiol 2010;298:L371-81.
21. Altemeier WA, Sinclair SE. Hyperoxia in the intensive care unit: why more is not always better. Curr Opin Crit Care 2007;13:73-8.
22. Knight PR, Kurek C, Davidson BA, et al. Acid aspiration increases sensitivity to increased ambient oxygen concentrations. Am J Physiol Lung Cell Mol Physiol 2000;278:L1240-7.
23. Matthay MA, Zimmerman GA. Acute lung injury and the acute respiratory distress syndrome: four decades of inquiry into pathogenesis and rational management. Am J Respir Cell Mol Biol 2005;33:319-27.
24. Thiel M, Chouker A, Ohta A, et al. Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury. PLoS Biol 2005;3:e174.
25. Farquhar H, Weatherall M, Wijesinghe M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J 2009;158:371-7.
26. Anderson KJ, Harten JM, Booth MG, et al. The cardiovascular effects of normobaric hyperoxia in patients with heart rate fixed by permanent pacemaker. Anaesthesia 2010;65:167-71.
27. Anderson KJ, Harten JM, Booth MG, et al. The cardiovascular effects of inspired oxygen fraction in

anaesthetized patients. Eur J Anaesthesiol 2005;22:420-5.
28. Severinghaus JW. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol Respir Environ Exerc Physiol 1979;46:599-602.
29. Mezidi M, Guérin C. Conservative versus liberal oxygenation targets for mechanically ventilated patients-a pilot multicenter randomized controlled trial. J Thorac Dis 2016;8:307-10.
30. Schulze A, Whyte RK, Way RC, et al. Effect of the arterial oxygenation level on cardiac output, oxygen extraction, and oxygen consumption in low birth weight infants receiving mechanical ventilation. J Pediatr 1995;126:777-84.
31. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-22.
32. Alía I, Esteban A, Gordo F, et al. A randomized and controlled trial of the effect of treatment aimed at maximizing oxygen delivery in patients with severe sepsis or septic shock. Chest 1999;115:453-61.

Cite this article as: Panwar R. The unknowns about oxygen therapy in critically ill patients. J Thorac Dis 2016;8(11):E1543-E1546. doi: 10.21037/jtd.2016.11.85