

# Change is in the air: dying to breathe oxygen in acute respiratory distress syndrome?

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Comment on: Aggarwal NR, Brower RG, Hager DN, *et al.* Oxygen Exposure Resulting in Arterial Oxygen Tensions Above the Protocol Goal Was Associated With Worse Clinical Outcomes in Acute Respiratory Distress Syndrome. *Crit Care Med* 2018;46:517-24.

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## Background

### Introduction

It is over 50 years since the first description of the acute respiratory distress syndrome (ARDS) (1), yet few topics have so exercised the imagination and efforts of the critical care research community. While substantial advances have been made in understanding the pathogenesis of ARDS, and several attempts have been made to develop pharmacological therapies for this common condition, understandably a large part of the focus has remained on optimizing mechanical ventilation to reduce iatrogenic lung injury (2,3). This journey has been marked by successes, most notably development of low tidal volume ventilation strategies (4), but remains a complex area of practice ripe for further improvement (5). Aggarwal *et al.* present a study that seeks to identify a new area where such improvement may be possible—titration of inspired fraction of oxygen (6).

### Oxygen: friend or foe

Sometime around 2.5 billion years ago, the earth began a roller coaster ride transition from an oxygen poor to oxygen rich atmosphere (7), and the availability of molecular oxygen as an electron acceptor in energy-efficient metabolic pathways was probably a major driver of the evolution of complex eukaryotic life (8). Indeed, since reduction of carbon-based fuels to generate ATP by

oxidative phosphorylation in mitochondria is the primary means of energy production in humans, oxygen is often viewed as the essence of human life. However, oxygen is a double-edged sword. The generation of reactive oxygen species (ROS) either as by-products of aerobic metabolism or by specialised enzymes, can damage important cellular molecules including proteins, lipid and DNA. Indeed all aerobic species possess highly conserved cellular defence strategies to deal with ROS (9), a dark threat that life has been battling since its emergence on the planet (10).

### Direct lung toxicity

It has long been understood that supra-normal partial pressures of inspired oxygen may injure lung tissue (11). Healthy human volunteers have been shown to develop mucociliary dysfunction and other features of tracheobronchitis after as little as 3 hours of inhaling 90–100 per cent oxygen gas mixtures. Comprehensive pathological and biochemical models of oxygen-related lung toxicity have been elaborated from animal models (12), and include both direct cell damage from ROS production, and subsequent activation of various inflammatory pathways.

In terms of the concentration of inspired oxygen required to produce toxicity, a series of animal experiments in the last century demonstrated convincingly that prolonged exposure to an  $\text{FiO}_2 \geq 0.7$  was unambiguously toxic to several animal species, and virtually all experiments find that most animals

die several days after breathing an  $\text{FiO}_2 \geq 0.8$  (12). The effect increases with increasing partial pressure, though toxicity has not been observed in general with  $\text{FiO}_2 < 0.6$ . The time course is further modulated by animal age, species and even strain. Therefore, direct lung toxicity from oxygen seems to begin as  $\text{FiO}_2$  is increased above 0.6 and develop as function of precise partial pressure, exposure time and host factors.

The histopathological changes induced in primates exposed to high inspired fractions of oxygen are very similar to those observed in the lungs of patients with ARDS who died without being exposed to high inspired concentrations of oxygen. These features include an early “exudative” phase progressing to a late “proliferative” or “fibrotic” phase (13,14). The close resemblance between hyperoxia induced lung injury and ARDS from other causes is alarming, because it raises the prospect that iatrogenic injury may become shrouded in a cloak of initiating pathology in severe ARDS and go unrecognized in clinical practice.

### *Systemic effects of hyperoxia*

Apart from direct toxicity from lung exposure to high fractions of inspired oxygen, if this exposure also leads to supraphysiological partial pressures of oxygen in the bloodstream, there is the potential for distal organ injury. For example, arterial hyperoxia has been shown to be associated with vasoconstriction in important vascular beds, such as in the coronary and cerebral circulation (15), and with a reduction in cardiac output (16). Similarly hyperoxia has been shown to cause remote injury in the eye, the central nervous system and the gastrointestinal tract (17), due to ROS mediated cell injury and subsequent inflammatory responses, though in truth the situation is complex and animal data have sometimes indicated a benefit of hyperoxemia through complex mechanisms including anti-inflammatory effects in certain models of shock states (18).

### *Clinical studies*

Surprisingly little randomised evidence exists to guide clinicians in deciding what represents a “safe” level of oxygen administration, particularly in mechanically ventilated patients (19). A recently published meta-analysis of RCTs comparing “liberal” to “conservative” oxygen administration strategies in various clinical scenarios concluded that there was a consistent signal for increased mortality overall with “liberal” oxygen administration (20). With a plausible pathobiology involving both direct

pulmonary and systemic effects in ARDS—could oxygen be particularly harmful in this patient group?

### **Current study**

This background provides the context for the interesting retrospective analysis presented by Aggarwal *et al.* which examines the association between “above goal” oxygen exposure and clinical outcomes in mechanically ventilated patients with ARDS (6).

### *Population*

The population examined was a cohort of patients with ARDS (American-European consensus definition) enrolled in a series of ten randomised controlled trials conducted by the ARDSnet group between 1996 and 2013. The authors excluded those assigned to receive targeted tidal volumes of 12 mL/kg of predicted body weight, as well as those in whom initial severity of ARDS could not be determined because they did not have an ABG on day 0 to define severity. This strategy yielded a total of 2,994 patients for analysis in this retrospective cohort study, or 69% of all those enrolled in the original ten trials. The exclusion criteria seem fair. Baseline severity of ARDS is a very plausible confounder in this study, and it seems reasonable to restrict analysis to cases where it can be accounted for. This is further supported by similar age, sex, and mean APACHE III scores in those who did not have a day 0 ABG and those who did. On the other hand, it is possible that this strategy affected the point estimate obtained, which might not be reflective of the true effect in all-comers eligible for the original trials.

### *Exposure*

The exposure of interest was oxygen administration greater than that necessary to achieve the oxygenation target laid out in the ARDSnet common protocols, which the authors termed “above goal” oxygen exposure. Participants were classified as having “above goal” oxygen exposure on a given day if they had a recorded  $\text{PaO}_2$  greater than 80 mmHg from altitude-adjusted morning arterial blood gases (ABGs). The magnitude of the exposure for a given day was calculated as the difference between morning  $\text{FiO}_2$  (at the time of ABG measurement) and 0.5 and cumulative exposure over the first 5 days was calculated by summation. This is a pragmatic and reasonable exposure definition. Really, we are interested in the effect on outcome of the

difference between the  $\text{FiO}_2$  used and the minimum  $\text{FiO}_2$  that could have been used to achieve a  $\text{PaO}_2$  within the protocolized target range, but of course could not be calculated retrospectively from the ARDSnet data. This said, the definition leads inevitably to some possibility of misclassification error. For example, oxygen administration is likely to be dynamic over the course of any given day, so the measure is an imperfect “snapshot” of inhaled oxygen exposure on a given day. Indeed, perhaps surprisingly given the focus on gas exchange in ARDS, not all patients had a morning ABG on each study day, forcing the investigators to extrapolate missing data from recorded data. Reassuringly, sensitivity analyses suggested that this was reasonable. Finally, although one could criticize the choice of an  $\text{FiO}_2$  of 0.5 as a “threshold” value in assessment of the magnitude of excess oxygen administration, a sensitivity analysis using different thresholds appeared not to alter the study conclusions significantly.

### Outcomes

The primary outcome was mortality prior to discharge home at 90 days. Secondary outcomes included ventilator free days (VFDs) and hospital-free days (HFDs). These measures are reassuringly robust, patient-centred and are closely aligned with primary and secondary outcomes of the original studies so that they are likely to be measured with similarly good precision. On the other hand, because of the retrospective nature of the study, unfortunately the authors were not able to assess some important secondary outcomes, particularly cognitive function and quality of life. This might be important because it has been argued that conservative oxygenation strategies in mechanically ventilated patient might be associated with a higher risk of hypoxemia, which in turn might affect cognitive function through increased frequency of injurious cerebral hypoxia. Indeed, where gas exchange is tenuous as it is in ARDS, this seems especially plausible and poorer oxygenation is associated with worse cognitive outcomes in ARDS (21). It would be important to know whether any favourable change in mortality related to a given oxygen administration strategy is counterbalanced by unfavourable changes in disability in survivors, since survival with a poor quality of life or severe disability may not be acceptable to some patients.

### Results

Even in the heavily protocolized mechanical ventilation

practice of the ARDSnet trials, above goal oxygen exposure was very common, occurring in almost half (48%) of patients. The authors observed a strong association between the exposure and their selected outcomes. In a multivariable regression model, cumulative above goal oxygen exposure was associated with an adjusted interquartile range odds ratio of in-hospital mortality at 90 days of 1.20 (95% CI: 1.11 to 1.31). Importantly, the magnitude of the effect on mortality is similar to that described in a recent meta-analysis comparing conservative to liberal oxygenation strategies in a wide variety of clinical scenarios (22). Though we are not told how exactly the authors selected variables for inclusion in the model, they seem to have included most of the critical confounders including age, sex, APACHE III score, PEEP and most importantly, baseline ARDS severity. Similarly, linear regression modelling using the same variables demonstrated that above goal oxygen exposure was associated with a reduction in VFDs of 0.83 (95% CI: 1.17 to 0.48) and a reduction in HFDs of 1.38 days (95% CI: 2.09 to 0.68).

### Caveats

What are we to make of these results? Firstly, the results of this study should be viewed as hypothesis generating not confirming and indeed the authors conclude this in their discussion. While the authors have made every attempt to control for it, the possibility of unmeasured or poorly measured confounding remains due to the observational nature of the work. As clinicians we can ask the question – what reasons might there be for a patient to experience above goal oxygen exposure in an experiment where mechanical ventilation is strongly protocol orientated? One possibility is that it is simply inattention to detail, or failure to adhere to the expected standard of care. If so, protocol violation might simply be a surrogate for poor care through a variety of mechanisms such as inadequate training, resourcing, or skill of the multidisciplinary team looking after the patient. Indeed, this is the strongest threat to the study conclusions. The association of above goal oxygen exposure with increasing hypotension is also interesting. Could it be that teams aim for higher oxygenation targets when continuous non-invasive oxygenation monitors fail because of peripheral vasoconstriction in hypotension. It is certainly plausible that carers might fear recognition of hypoxemia will be delayed in such circumstances. If so does the association simply represent confounding by co-morbid pathology such as shock? Finally, baseline ARDS severity

classification has been shown to poorly predict subsequent disease progression (23)—could it be that the association simply represents indication bias due to failure to capture differences in ARDS disease severity? And similarly, while APACHE III is a good measure of overall critical illness severity, it is imperfect. Is it possible that when care needs are complex, healthcare workers default to hyperoxia to eliminate one variable contributing to cognitive load and care burden in order to focus on other elements of care? If so then above goal oxygen exposure may simply represent a marker for “sicker” patients.

These are minor quibbles with a well conducted observational study that demonstrates a strong association in a clinical setting between above goal oxygen administration and poorer outcomes in ARDS, a hypothesis that has a sound theoretical underpinning. The answer to the question of whether this represents a real and important effect in ARDS patients will ultimately only come from randomised controlled experiments that include this population. We agree with the authors that their data adds further weight to a theory and set of premises that need to be urgently and comprehensively investigated in such randomised controlled trials—ICU ROX (24), oxyPICU (25) and HOT-ICU (NCT03174002) for example. If these experiments support the conclusions of Aggarwal *et al.* we may well have to add “hyperoxia” alarms to the symphony of intensive care!

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References

- Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet* 1967;2:319-23.
- Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med* 2017;377:562-72.
- Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome. *JAMA* 2018;319:698-710.
- Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, et al. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med* 2000;342:1301-8.
- Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315:788-800.
- Aggarwal NR, Brower RG, Hager DN, et al. Oxygen Exposure Resulting in Arterial Oxygen Tensions Above the Protocol Goal Was Associated With Worse Clinical Outcomes in Acute Respiratory Distress Syndrome. *Crit Care Med* 2018;46:517-24.
- Lyons TW, Reinhard CT, Planavsky NJ. The rise of oxygen in Earth's early ocean and atmosphere. *Nature* 2014;506:307-15.
- Thannickal VJ. Oxygen in the evolution of complex life and the price we pay. *Am J Respir Cell Mol Biol* 2009;40:507-10.
- Birben E, Sahiner UM, Sackesen C, et al. Oxidative stress and antioxidant defense. *World Allergy Organ J* 2012;5:9-19.
- Briehl MM. Oxygen in human health from life to death—An approach to teaching redox biology and signaling to graduate and medical students. *Redox Biol* 2015;5:124-39.
- Jackson RM. Pulmonary oxygen toxicity. *Chest* 1985;88:900-5.
- Kallet RH, Matthay MA. Hyperoxic acute lung injury. *Respir Care* 2013;58:123-41.
- Wolfe WG, Robinson LA, Moran JF, et al. Reversible pulmonary oxygen toxicity in the primate. *Ann Surg* 1978;188:530-43.
- Bachofen M, Weibel ER. Alterations of the Gas Exchange Apparatus in Adult Respiratory Insufficiency Associated with Septicemia 1, 2. *Am Rev Respir Dis* 1977;116:589-615.
- Bak Z, Sjöberg F, Rousseau A, et al. Human cardiovascular dose? Response to supplemental oxygen. *Acta Physiol (Oxf)* 2007;191:15-24.
- Waring WS, Thomson AJ, Adwani SH, et al. Cardiovascular effects of acute oxygen administration in healthy adults. *J Cardiovasc Pharmacol* 2003;42:245-50.
- Bostek CC. Oxygen toxicity: an introduction. *AANA J* 1989;57:231-7.
- Asfar P, Calzia E, Huber-Lang M, et al. Hyperoxia During Septic Shock—Dr. Jekyll or Mr. Hyde? *Shock* 2012;37:122-3.
- Damiani E, Donati A, Girardis M. Oxygen in the critically ill. *Curr Opin Anaesthesiol* 2018;31:129-35.
- Young P, Bailey M, Beasley R, et al. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury

- Among Patients in the Intensive Care Unit. *JAMA* 2015;314:1701-10.
21. Mikkelsen ME, Christie JD, Lanken PN, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study. *Am J Respir Crit Care Med* 2012;185:1307-15.
  22. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391:1693-705.
  23. Hernu R, Wallet F, Thiollière F, et al. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. *Intensive Care Med* 2013;39:2161-70.
  24. Mackle DM, Bailey MJ, Beasley RW, et al. Protocol summary and statistical analysis plan for the intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX). *Crit Care Resusc* 2018;20:22-32.
  25. Jones GAL, Ramnarayan P, Raman S, et al. Protocol for a randomised pilot multiple centre trial of conservative versus liberal oxygenation targets in critically ill children (Oxy-PICU). *BMJ Open* 2017;7:e019253.

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