Editorial

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Oxygen therapy and the Goldilocks principle

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Whilst fundamental to human survival, oxygen is harmful in excess and it is possible that as intensive care specialists, we focus less attention on its use than might be expected by the public and patients who we treat.[1] In a clinical environment where it is rare to not administer oxygen to a patient, one would have presumed that we would be awash with evidence and guidance about its use. Surely decades of clear and indisputable findings must underpin how we use the most commonly administered drug in intensive care units the world over. Not so, it would seem. Huge variation in practice can be demonstrated[2,3] and whilst harder to quantify, there is undoubtedly a wide spectrum of beliefs underpinning this inconsistency. It is our belief that each and every patient requires careful assessment and individualised oxygen titration to achieved desired targets, rather than having a universal 'one-size-fits-all' prescription imposed upon them. What is lacking though is the evidence on which to base clinical guidance. Therefore, we find ourselves in an awkward position; both too little and too much oxygen is harmful. Yet currently we are uncertain what the right amount of oxygen is for individual critically ill patients.

The neurological consequences of hyperbaric oxygen toxicity were demonstrated by Paul Bert at the end of the 19th century[4] and the ED50 of oxygen has been estimated at 5.3 atmospheres (in mice).[5] Not long after Bert's work, James Lorrain Smith conducted a similar set of animal experiments focusing on how the lungs tolerate hyperoxia.[6] Unlike Bert though, Smith added in experimental conditions below one atmosphere in pressure, but with a greater oxygen partial pressure than room air. When two mice were place in 73.6% of an atmosphere of oxygen, he reported that '*On the fourth day of the experiment, one mouse was found dead, and when examined showed congestion and consolidation of the lungs*'. The other mouse survived to day nine but and then unfortunately died of an '*accidental cause*'. Similar results were seen at 79.9% of an atmosphere of oxygen; again, a 50% mortality rate was reported by day four. Smith made the following profound conclusion: '*The experiments just described show that at a tension a good deal higher than that of ordinary air, oxygen has the effect on the lungs of an irritant, and produces inflammation*'. These words echoed Joseph Priestly's statement of 1774 '*. . .for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast and the animal powers be too soon exhausted in this pure kind of air*'.[7] In the time that has passed since oxygen's discovery, our understanding of human physiology has expanded enormously and molecular biology techniques have opened our eyes to intricate but invisible biochemical mechanisms that govern what Smith observed over one hundred years ago. During oxidative phosphorylation, enzyme complexes on the inner mitochondrial membrane (primarily complex three, and to a lesser extent complex one) release superoxide radicals (O_2^-) from molecular oxygen (dioxygen). This source of endogenous reactive oxygen species (ROS) in turn forms hydrogen peroxide (H_2O_2) and the hydroxyl radical (·OH). At low concentration, these molecules perform vital messenger roles, including cellular oxygen sensing, but in excess, they have destructive qualities leading to breakdown of mitochondrial DNA and membrane structures, then cellular DNA, protein and lipids. The law of mass action dictates that increasing oxygen availability to the respiratory chain produces more ROS: raising the ambient partial pressure of oxygen from <4 kPa to as little as 10 kPa in a cell culture environment increases H_2O_2 production several hundred fold.[8] These findings readily explain Smith's 50% murine mortality rate at an equivalent oxygen concentration of greater than approximately 70%.

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The majority of drugs with a narrow therapeutic index are carefully titrated according to some measure of drug level or effectiveness. Considerable time and resources are invested in ensuring the optimum dose of insulin, heparin, aminoglycoside antibiotics, immunosuppressants, anticonvulsants, and antiarrhythmics, amongst many others. To some extent, we pay respect to this paradigm when administering oxygen by measuring peripheral oxygen saturation (SpO_2) and the arterial partial pressure of oxygen (PaO_2). But perhaps because this 'drug' is also abundant in the air we breathe (20.95% of it currently[9]), we may have become complacent in the way that we titrate it. Rightly or wrongly, our fear of hypoxaemia far outweighs our appreciation of the harmful effects of hyperoxaemia, which tends to lead to prescriptions that reflect this prejudice, for example 'maintain SaO_2 >95%' or 'PaO_2 >8 kPa'. Furthermore, the ceiling effect inherent in pulse oximetry may further contribute to this tendency to hyperoxaemia: a low SaO_2 clearly indicates hypoxaemia, but an SaO_2 of 100% is consistent with a PaO_2 as low as 14 kPa or as high as >80 kPa. Is this precision medicine in the 21st century?

Over the last few years, a number of specialties have reconsidered oxygen therapy for a range of conditions, bringing into question the traditional approach that if all else fails, just make sure you give oxygen, and plenty of it. For decades, we chose to ignore the fundamental physiological principle that hyperoxaemia leads to profound coronary artery vasoconstriction and persevered with the intuitively appealing (but fundamentally incorrect) notion that providing high concentration oxygen to patients with an acute myocardial infarction would increase the amount of oxygen delivered to the myocardium and preserve cellular metabolic homeostasis. Any physiology undergraduate of worth might have spotted the flaw in this well-intended strategy – increasing the fractional inspired oxygen concentration (FIO_2) from 0.21 to 1.0 only raises arterial oxygen content by a small proportion (because haemoglobin is already nearly fully saturated). This century old practice has, until recently, not been vigorously challenged despite a publication in JAMA in 1950 suggesting that administering 100% oxygen to patients with myocardial infarction or angina pectoris could be harmful.[10] Many other expert commentators have also held this view and it is only since publication of the AVOID trial in 2015, that practice is finally changing to reduce unnecessary exposure to supplemental oxygen.[11]

So where are we today in terms of oxygen use in the critically ill? It would appear that a recent surge in interest has moved us forwards, but there remains a long way to go. Retrospective analysis of critical care data has shown that hyperoxaemia is potentially harmful in a number of conditions commonly dealt with on our units.[12,13] Whilst it may be challenging to test the causal nature of this relationship in a randomised prospective manner, it is important that we take on this challenge for the benefit of future patients. Given the wealth of observational data suggesting harm from hyperoxaemia and the epidemiological data suggesting that this is commonplace in clinical practice, we must overcome concerns about the ethics of deliberately exposing patients to higher levels of inspired oxygen. Moreover, the concept of 'permissive hypoxaemia' has undergone some preliminary exploration and thus far has been shown to be both feasible and safe.[14–16] Allowing critically ill patients to be managed with an SpO_2 lower than usually tolerated (commonly in the range of 88–92%) would therefore appear to merit further investigation on a larger scale. Two studies that are currently in progress are attempting to address this and their results will be of great value in an area of our practice that is otherwise devoid of evidence. One recently published study requires more than a passing mention. In a single centre study conducted in Italy over approximately two and a half years, critically ill patients were randomised into one of two oxygenation groups.[17]. The 'conservative' oxygenation group had their PaO_2 maintained between 9.3 and 13.3 kPa or an SpO_2 of 94%–98%, whilst the control group conformed to 'standard ICU practice' defined as a PaO_2 up to 20 kPa or SpO_2 values between 97% and 100%. In the control group, oxygen was administered at a minimum FIO_2 of 0.4 and if SpO_2 fell below 95%–97%, the FIO_2 was increased to reach the target value of SpO_2. A total of 434 patients were studied and included in a 'modified intent-to-treat analysis'. The investigators achieved good separation of oxygenation between the two study cohorts, with a daily time-weighted PaO_2 averages of 13.6 kPa in the standard group and 11.6 kPa in the conservative group. The primary outcome of this study was ICU mortality, and the values reported were: 11.6% in the conservative group and 20.2% in the conventional group, giving an absolute risk reduction of 8.6% (1.7–15.0%). Impressive figures for such a simple intervention, comparable to those achieved in van den Berghe et al.'s[18] intensive insulin therapy and Rivers et al.'s goal-directed therapy studies.[19] However, the 'modified intent-to-treat' method used in this study involved only analysing data from those patients receiving the intervention for greater than 72 h, therefore excluding some patients post-randomisation and introducing a significant source of bias into the study results. Other issues raised in an editorial that accompanied the publication of this study include: baseline imbalances between groups at the time of randomisation favouring the conservative oxygen group; early termination of the study following an unplanned interim analysis; and the low ratio of event to participants in each group (25/216 deaths in the conservative group), increasing the likelihood of a false-positive result.[20] Perhaps, though, the most pertinent thing

to consider is whether 13.6 kPa vs. 11.6 kPa is a study of permissive hypoxaemia, or one of permissive hyperoxaemia. It should be highlighted that the authors completed this study in the face of huge adversity, as an earthquake caused substantial damage to the hospital in which participants were being recruited from.[17]

Conclusion

The life cycle of many critical care interventions to support physiology follows a predictable pattern. Initial excitement about life-saving potential, linked with the logic that if a bit of something is good, then more may well be better, leads to widespread and aggressive adoption. Time, experience and clinical trials data result in moderation of this approach over time, such that we arrive at a point where we avoid both excessive and inadequate therapy. Excellent examples of this phenomenon include renal replacement therapy, target arterial carbon dioxide levels and tidal volumes used in mechanical ventilation; in each case, we have moved to a more measured approach. Perhaps, we are now in the process of following this same path for oxygen therapy, moving away from the notion that more is always better, and instead giving the least amount necessary, thereby avoiding the harms associated with excess and inadequate therapy. Like Goldilocks, we need to avoid too much and too little oxygen, and aim for 'just right'.

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References

1. Doward J. Doctors are told to curb overuse of oxygen in hospitals. *The Guardian*, https://www.theguardian.com/society/2016/may/14/doctors-oxygen-overuse-hospitals-nhs-lung-patients-dangers (2016, accessed 17 May 2017).
2. Eastwood GM, Reade MC, Peck L, et al. Critical care nurses' opinion and self-reported practice of oxygen therapy: a survey. *Aust Crit Care* 2011; 25: 23–30.
3. Eastwood GM, Reade MC, Peck L, et al. Intensivists' opinion and self-reported practice of oxygen therapy. *Anaesth Intensive Care* 2011; 39: 122–126.
4. Bert P. *La pression barométrique: Recherches de physiologie expérimentale*. Paris: Masson, 1878.
5. Smith RA, and Paton WD. The anesthetic effect of oxygen. *Anesth Analg* 1976; 55: 734–736.
6. Smith JL. The pathological effects due to increase of oxygen tension in the air breathed. *J Physiol* 1899; 24: 19–35.
7. Priestley J. *Experiments and observations on different kinds of air*. London: W. Bowyer and J. Nichols, 1774.
8. Fandrey J, Frede S, and Jelkmann W. Role of hydrogen peroxide in hypoxia-induced erythropoietin production. *Biochem J* 1994; 303: 507–510.
9. Martin D, McKenna H, and Livina V. The human physiological impact of global deoxygenation. *J Physiol Sci* 2017; 67: 97–106.
10. Russek HI, Regan FD, and Naegele CF. One hundred percent oxygen in the treatment of acute myocardial infarction and severe angina pectoris. *J Am Med Assoc* 1950; 144: 373–375.
11. Stub D, Smith K, Bernard S, et al. Air versus oxygen in ST-segment-elevation myocardial infarction. *Circulation* 2015; 131: 2143–2150.
12. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, et al. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, metaanalysis, and meta-regression of cohort studies. *Crit Care Med* 2015; 43: 1508–1519.
13. 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.
14. 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.
15. Suzuki S, Eastwood G, Glassford N, et al. Conservative oxygen therapy in mechanically ventilated patients: a pilot before-and-after trial. *Crit Care Med* 2014; 42: 1414–1422.
16. Helmerhorst HJ, Schultz MJ, van der Voort PH, et al. Effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in critically ill patients: a before and after trial. *Crit Care Med* 2016; 44: 554–563.
17. Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA* 2016; 316: 1583–1589.
18. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359–1367.
19. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368–1377.
20. Ferguson ND. Oxygen in the ICU: too much of a good thing. *JAMA* 2016; 316: 1553–1554.