2023-05

Is the U-shaped curve still of relevance to oxygenation of critically ill patients?

Martin, Daniel

10.1007/s00134-023-07014-x
Intensive Care Medicine
Springer Science and Business Media LLC

What's New in Intensive Care?

Is the U-shaped curve still of relevance to oxygenation of critically ill patients? A literature update.

Daniel Martin[1,2], Audrey de Jong[3] and Peter Radermacher[4]

1. Peninsula Medical School, University of Plymouth, John Bull Building, Tamar Science Park, Plymouth, PL6 8BU, United Kingdom
2. Intensive Care Unit, University Hospitals Plymouth, Derriford Road, Plymouth, Devon, PL6 8DH, United Kingdom
3. Department of Anaesthesia and Intensive Care unit, Regional University Hospital of Montpellier, St-Eloi Hospital, University of Montpellier, PhyMedExp, INSERM U1046, CNRS UMR, 9214, Montpellier, CEDEX 5, France.
4. Institut für Anästhesiologische Pathophysiologie und Verfahrensentwicklung, Universitätsklinikum, Helmholtzstrasse 8-1, 89081 Ulm, Germany

Virtually every drug has an effective and toxic dose and oxygen is no exception. Molecular oxygen has been referred to as "*janus-headed*", inasmuch as it is vital for mitochondrial respiration and toxic due to formation of reactive oxygen species (ROS). ROS share the "*friend and foe character*", being both toxic and vital for host defence mechanisms [1]. Over 90% of oxygen consumption is used for adenosine triphosphate production via mitochondrial oxidative phosphorylation; however, approximately 1–3% of the oxygen consumption is utilised at complexes I and III of the electron transport chain to generate superoxide anions. Whilst ROS play a vital role in numerous homeostatic mechanisms, in excess these molecules can cause substantial harm to the framework of cells. Hyperoxia increases the rate of superoxide anion production [2] and once our innate antioxidant systems become overwhelmed, oxidative damage occurs. Severe hypoxia can lead to bioenergetic failure and cell death, but paradoxically, moderate hypoxia can also initiate an increase mitochondrial ROS production. Thus, both hyperoxia and hypoxia can initiate oxidative damage and a pro-inflammatory reaction. This is particularly pronounced during ischaemia-reperfusion injury (e.g. resuscitation after cardiac arrest) and/or disturbed cellular oxygen utilisation (e.g. sepsis). Consequently, hyperoxia normally exacerbates ischaemia-reperfusion reperfusion injury. Lung parenchyma is especially vulnerable to oxidative damage and this pulmonary oxygen toxicity usually presents as pneumonitis, eventually leading to haemorrhagic pulmonary oedema. Given this inescapable biological framework, it is vital that we administer the right dose of oxygen (neither too little or too much) to critically ill patients, in order to minimise the harm this potentially lethal drug may cause them.

In the recently published PILOT (Pragmatic Investigation of Optimal Oxygen Targets) trial the authors stated that their findings did not support the existence of a U-shaped relationship between oxygenation and clinical outcomes [3]. But was their conclusion correct? The possible existence of this curvilinear relationship has been discussed in the literature for many years [4]. Although not illustrated as a curve, data collected between 2001-5 from 6326 patients admitted to intensive care units (ICUs) in 120 hospitals in the US showed that in-hospital mortality post-cardiac arrest was lowest amongst patients in whom the first arterial blood gas (ABG) obtained in the ICU demonstrated normoxaemia, rather than hypoxaemia or hyperoxaemia (45%, 57% and 63% respectively) [5]. In a similar study, oxygenation data consisting of 295,079 ABG analyses from 14,441 patients admitted to three ICUs in the Netherlands between 2011-14 were used to construct a curve of adjusted probability of in-hospital death by mean PaO_2 [6]. The authors presented evidence for a relationship between supraphysiologic arterial oxygen levels and hospital mortality; a finding both confirmed [7] and refuted [8] in other retrospective analyses. Whilst retrospective studies such as these are useful for highlighting potential associations, prospective randomised trials are the only way to truly establish a causal relationship between oxygenation and outcomes.

Any U-shaped curve is derived from a bimodal distribution with frequencies that steadily fall and rise. Many associations between two variables can be captured by a U-shaped curve, such as the one between oxygen administration and mortality, which can be supported by the pathophysiology detailed above. However, the statistical methods, either parametric or non-parametric, used to establish a U-shaped relationship, rely on accurate and reliable data. Some limitations associated

with retrospective studies that were used to establish the U-shaped associations between oxygen administration and mortality should be underlined in this context. For example, sickest patients tend to get given more oxygen; therefore, in a retrospective study, it will often look like high oxygen levels are associated with high mortality. Regarding the U-shaped curve association between oxygen levels and mortality derived from retrospective studies, we are probably facing the classic *association* but not *causation* scenario. All of the adjustment methods are imperfect, even when modern statistical adjustment is well-performed. Large multicentre retrospective studies derived from databases are subjected to residual confounding and imprecision of data recorded. Lower sample size single centre studies are subjected to potential imbalance of prognostic factors between patients receiving low, '*normal'* or high levels of oxygen. Additionally, all retrospective studies are likely to have temporal biases, between oxygen administration and outcome, as oxygen administration precedes the outcome. When assessing mortality in patients having received oxygen during invasive mechanical ventilation, mortality and oxygen administration have already occurred at the time of study initiation. Therefore, only findings from randomised controlled trials should be used to draw an unbiased U-shaped curve between oxygen administration and mortality.

Several trials of conservative oxygen therapy (COT) have now been conducted in critically ill patients, and whilst their combined findings suggest no overall signal of benefit or harm, there is considerable heterogeneity in their design and conduct [9]. By selecting different sub-populations of critically ill patients, imposing varied oxygenation targets for both the COT and comparator groups, and achieving incomparable measured arterial oxygenation levels, it is difficult to draw clear

conclusions from what has been published to date. If one assumes the thesis that a U-shaped curve does exist [6] then we must try to place the findings of recent trials within that curve to confirm its existence. In Figure 1, data from recent randomised trials have been superimposed on a U-shaped curve; arrows depict the approximate achieved arterial oxygenation between lower and higher target groups in trials recruiting mixed critically ill patients. These clinically relevant oxygenation ranges only really account for a very small section of the central part of the curve and perhaps serve to flatten its nadir a little. Taken out of context one might conclude that there is little or no difference in clinical outcomes between higher and lower oxygenation targets in critical illness, and as such that the excessive administration of oxygen is safe. With the exception of one trial [10] most of these trials did not evaluate oxygenation targets outside of the range of approximately 9.2-13.8 kPa. In the one trial that breached this threshold, the authors reported an increased incidence of serious adverse events in the hyperoxia group [10]. Conversely, one included trial reported a reduction in ICU mortality in those allocated to COT [11].

In summary, the interpretation of retrospective studies in this field is fraught with challenges that limit our ability to form reliable conclusions from them. Current prospective clinical trials data can neither corroborate or refute the existence of the proposed U-shaped relationship between oxygen and outcomes in critically ill patients seen in some retrospective datasets. Recent findings from randomised trials have failed to enlighten us further.

Conflicts of interest

DM: Chief investigator of the UK-ROX trial (Evaluating the clinical and cost-effectiveness of a conservative approach to oxygen therapy for invasively ventilated adults in intensive care). NIHR130508.

ADJ: Received honoraria from Medtronic, Drager and Fisher-Paykel.

PR: supported by the Deutsche Forschungsgemeinschaft (CRC 1149; project number 251293561).

Figure 1. A conceptual depiction of the proposed U-shaped relationship between arterial oxygenation and mortality in critically ill patients.

The curve was adapted from Helmerhorst et al.'s graph of adjusted probability of in-hospital death by mean PaO_2 [6]. Additional findings (within the box) were superimposed from the trials included in a recent systematic review [9–16] and those published subsequently to it [3, 17]. Only trials that enrolled a mixed general ICU population were included. The inset box shows the difference between the reported (or approximated) achieved arterial oxygenation values in the intervention and comparator groups of each trial (represented by each arrow-head). Orange arrows denote trials with no difference in the primary outcome measure between lower and higher oxygenation levels; the green arrow denotes a trial in which lower oxygenation was favourable; the red arrow denotes a trial that was halted early due to safety concerns in the higher oxygenation group.

References

1. Magder S (2006) Reactive oxygen species: toxic molecules or spark of life? Crit Care 10:208. https://doi.org/10.1186/cc3992

2. Singer M, Young PJ, Laffey JG, et al (2021) Dangers of hyperoxia. Crit Care 25:440. https://doi.org/10.1186/s13054-021-03815-y

3. Semler MW, Casey JD, Lloyd BD, et al (2022) Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation. N Engl J Med. https://doi.org/10.1056/NEJMoa2208415

4. Martin DS, Grocott MPW (2013) Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. Crit Care Med 41:423–432. https://doi.org/10.1097/CCM.0b013e31826a44f6

5. Kilgannon JH, Jones AE, Shapiro NI, et al (2010) Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA 303:2165–2171. https://doi.org/10.1001/jama.2010.707

6. Helmerhorst HJF, Arts DL, Schultz MJ, et al (2017) Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. Crit Care Med 45:187–195. https://doi.org/10.1097/CCM.0000000000002084

7. Palmer E, Post B, Klapaukh R, et al (2019) The Association between Supraphysiologic Arterial Oxygen Levels and Mortality in Critically Ill Patients. A Multicenter Observational Cohort Study. Am J Respir Crit Care Med 200:1373–1380. https://doi.org/10.1164/rccm.201904-0849OC

8. Eastwood G, Bellomo R, Bailey M, et al (2012) Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med 38:91–98. https://doi.org/10.1007/s00134-011-2419-6

9. Chen X-L, Zhang B-L, Meng C, et al (2021) Conservative oxygen therapy for critically ill patients: a meta-analysis of randomized controlled trials. J Intensive Care Med 9:47. https://doi.org/10.1186/s40560-021-00563-7

10. Asfar P, Schortgen F, Boisramé-Helms J, et al (2017) Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med 5:180–190. https://doi.org/10.1016/S2213-2600(17)30046-2

11. Girardis M, Busani S, Damiani E, et al (2016) Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. JAMA 316:1583–1589. https://doi.org/10.1001/jama.2016.11993

12. Schjørring OL, Klitgaard TL, Perner A, et al (2021) Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. N Engl J Med 384:1301–1311. https://doi.org/10.1056/NEJMoa2032510

13. Barrot L, Asfar P, Mauny F, et al (2020) Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. N Engl J Med 382:999–1008. https://doi.org/10.1056/NEJMoa1916431

14. Yang X, Shang Y, Yuan S (2019) Low versus high pulse oxygen saturation directed oxygen therapy in critically ill patients: a randomized controlled pilot study. J Thorac Dis 11:4234–4240. https://doi.org/10.21037/jtd.2019.09.66

15. ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group, Mackle D, Bellomo R, et al (2020) Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med 382:989–998. https://doi.org/10.1056/NEJMoa1903297

16. Panwar R, Hardie M, Bellomo R, et al (2016) Conservative versus Liberal Oxygenation Targets for Mechanically Ventilated Patients. A Pilot Multicenter Randomized Controlled Trial. Am J Respir Crit Care Med 193:43–51. https://doi.org/10.1164/rccm.201505-1019OC

17. Gelissen H, de Grooth H-J, Smulders Y, et al (2021) Effect of Low-Normal vs High-Normal Oxygenation Targets on Organ Dysfunction in Critically Ill Patients: A Randomized Clinical Trial. JAMA 326:940–948. https://doi.org/10.1001/jama.2021.13011