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Editorial

CON: Routine hyperoxygenation in adult surgical patients whose tracheas are intubated

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Atmospheric oxygen levels have been at a nearly stable fraction of 21% for the past 350 million years. This implies that respiratory mechanisms in eukaryotic cells have evolved exactly the same across all taxonomic rank of phyla including animals, plants and fungi. Humans, whose evolution started about 7 million years ago, have never been exposed to higher inspired oxygen concentrations. In the era of modern medicine, however, oxygen has become available as a drug that is commonly administered at supraphysiological levels by physicians (including anaesthetists) in a wide variety of clinical situations. In 2016, the World Health Organization (WHO) guideline for prevention of surgical site infections strongly recommended the routine use of hyperoxia ($F_IO_2 \geq 0.8$) for all surgical patients whose tracheas were intubated and, if feasible, for 2–6 h postoperatively. This recommendation generated considerable controversy, mainly amongst anaesthetists, leading to an early revision of the guideline in 2018. In this edition of the guidelines, the recommendation to use hyperoxygenation was weakened to 'conditional' [1]. Still, the discussion as to whether hyperoxygenation is beneficial is ongoing.

In this debate, we make two main arguments: the efficacy of hyperoxygenation to reduce surgical site infections; and the concern that hyperoxia may be harmful to other tissues and organs. We discuss the controversies surrounding hyperoxygenation in peri-operative care; argue that robust evidence for the routine use of peri-operative hyperoxia is lacking; and plea that surgical patients are not immune to the toxic effects associated with it.

Efficacy

The physiological concept behind the application of hyperoxygenation is improving neutrophilic action by promoting oxygen delivery to tissues. Indeed, it has been shown that oxidative killing of bacteria by neutrophils is logarithmically associated with tissue PO_2 and that it is significantly reduced below a tissue PO_2 of 5.3 kPa (40 mmHg), which is just below physiological values [2]. Oxygen delivery to tissues can be expressed as the product of blood flow and arterial oxygen content. Because most oxygen is bound to haemoglobin, tissue oxygen delivery is more effectively optimised by increasing blood flow (or cardiac output) than by increasing arterial PO_2. Indeed, arterial PO_2 must be higher than 40 kPa (300 mmHg) in order to significantly improve neutrophilic killing. Strikingly, this is also the level of arterial PO_2 that has been associated with a sharp increase in mortality in critically ill patients [3].

The efficacy of hyperoxygenation to reduce surgical site infections has been the subject of multiple randomised controlled trials that have been reviewed repeatedly. In the most recent meta-analysis, peri-operative hyperoxygenation did not significantly reduce the incidence of surgical site infections when compared with normoxia, OR (95%CI) 0.89 (0.73–1.08), p = 0.23 [4]. These findings were corroborated

in another methodologically robust trial that was published recently and showed no significant difference in the incidence of surgical site infections between an inspired oxygen fraction of 0.3 and 0.8 [5]. So far, over 13,000 patients have been randomly allocated to receive hyper- or normoxia [6] and still no clear benefit from hyperoxygenation has been shown. This strongly indicates that the risk for futility of any further study is high.

Looking at the studies included in the meta-analysis, three out of eleven found significant benefit from hyperoxygenation, whereas all remaining studies did not [7–9]. The study by Greif et al. was the first to suggest the benefit of hyperoxygenation [7]. It is interesting to note that this study was published in 2000, that is, before the era of goal-directed fluid therapy, which has been shown to decrease the incidence of surgical site infections considerably. Therefore, tissue oxygen delivery was not enhanced by optimising stroke volume and blood flow, and this may limit the transferability of these results to our current clinical practice. In addition, it is possible that supplemental oxygen is no longer effective because its benefits are masked by two decades of improved surgical techniques. The second study by Belda et al., as well as the third study by Myles et al. showed benefit for hyperoxygenation only by narrow margins [8, 9]. When the Fragility Index of these two trials is calculated to determine the statistical robustness of the findings, both trials score below the 10th percentile (with a fragility index of zero) [10]. Furthermore, the latter study did not investigate the effects of hyperoxygenation but rather compared anaesthesia using 70% N_2O and 30% O_2 with N_2O-free gas (80% O_2, 20% N_2) [9]. Therefore, the effects of hyperoxygenation were a secondary endpoint and, although the authors pointed out that their study was not designed to compare the effect of high versus low oxygen concentrations, their trial was not excluded from the meta-analysis.

Lastly, the largest available study to date by Kurz et al., published in 2018, was not included in the meta-analysis, because the authors pseudo-randomly assigned 5749 patients to either $F_IO_2 = 0.3$ or $F_IO_2 = 0.8$ in a 2-weekly alternating design instead of strictly randomising patients on a daily basis. The authors did not identify any benefit from hyperoxygenation on various patient outcomes including infections, anastomotic leakage or sepsis [11].

Potential harms

To assess the safety of peri-operative hyperoxia on clinical outcomes, the WHO performed a meta-analysis and concluded that no definite signal of harm from peri-operative hyperoxia was found [12]. However, it could be argued that this analysis was not adequately powered to detect serious adverse events, such as increased mortality, with sample sizes per outcome measure around 2000 patients. Larger series, such as the cohort of 73,922 patients published by Staehr-Rye et al., showed that various complications were positively associated with hyperoxia in a dose-dependent manner [13]. In this cohort, hyperoxia was associated with increased 30-day mortality, adjusted OR (95%CI) 1.97 (1.30–2.99). This finding was supported in a semi-randomised trial comprising 5749 patients that indicated that hyperoxygenation may increase mortality, relative risk (95%CI) 1.97 (0.71–5.47) $p = 0.08$ [11]. Another trial also indicated a possibly higher 180-day mortality in the hyperoxia group, relative risk (95%CI) 2.20 (0.97–5.01), $p = 0.08$ [5]. In addition, several meta-analyses have demonstrated increased risks of morbidity and mortality from hyperoxia during mechanical ventilation in patients undergoing emergency surgery or with traumatic brain injury, cardiac arrest and stroke, showing both a time- and dose-dependent effect [14, 15]. When we expand our views outside the operating theatre to assess the safety of sustained hyperoxygenation in prolonged mechanical ventilation, we observe a linear relationship between exposed time to hyperoxia and mortality in patients on the ICU [15]. Furthermore, this relationship between arterial hyperoxia and mortality is virtually unchanged in a subset of patients that were admitted to ICU postoperatively and whose lungs were ventilated < 12 h when data were adjusted for age, length of stay and risk. This may be pertinent for the WHO recommendation because the administration of hyperoxygenation is also recommended to be continued in the immediate postoperative period.

Apart from effects on clinical outcome, principal pathophysiological concepts determine the effects of hyperoxygenation on tissue level. The main pathways leading to harm in anaesthetised patients can be summarised as haemodynamic modulation, pulmonary alteration and oxidative stress. The resulting harmful effects are likely to depend on co-existing conditions and the duration and degree of the exposure to hyperoxia.

Cardiovascular effects

Haemodynamic changes are reflected by systemic vasoconstriction as plasma-dissolved oxygen acts as a nitric oxide scavenger via production of reactive oxygen species leading to increased peripheral resistance. Although this is not widely recognised, this could induce a significant increase in blood pressure and secondary bradycardia. Together, this may reduce cardiac output and blood flow through vital organs, thereby paradoxically compromising

perfusion and oxygen delivery. Indeed, MRI scans suggest that although arterial PO_2 increases during hyperoxia, oxygen delivery is reduced in cardiac tissue from arterial PO_2 levels ≥ 18 kPa [16]. Additionally, measurements on the microcirculation indicate worsened tissue (sub-lingual) perfusion with arterial PO_2 ≥20 kPa [17]. These effects may account for the known increase in early myocardial injury and a larger myocardial infarct size by supplemental oxygen during myocardial infarction and the increased long-term risk of myocardial infarction and other heart disease during peri-operative hyperoxia. Lastly, these vasoconstrictive effects can be intensified by secondary hypocarbia, caused by a reduced carbon dioxide carriage (the Haldane effect).

Anaesthetists commonly anticipate critical events; therefore, during airway management, deliberate hyperoxia is commonly employed. Although this practice serves the direct goal of optimising safety margins by increasing apnoea tolerance, this may lead to paradoxically decreased oxygen delivery in critical tissues described above due to the haemodynamic effects of supplemental oxygen. Indeed, pre-oxygenation may increase the time to haemoglobin desaturation, but underlying tissue oxygen delivery, which is not monitored, may be impaired. When hyperoxygenation is maintained throughout surgery, continuously high pulse oximetry saturations (with a ceiling effect) could mask problems with pulmonary ventilation and perfusion, and also tissue perfusion and oxygenation. Additionally, postoperative supplemental oxygen has been shown to decrease the incidence of desaturation, but to mask the occurrence of respiratory depression in patients treated with opioids or in patients with chronic lung disease [18]. Therefore, hyperoxygenation just before an anticipated critical event (pre-oxygenation) seems appropriate, but as soon as the likelihood of critical events decreases, prolonged oxygen administration with the goal to increase safety margins can be a superfluous intervention that conveys considerable risk.

Pulmonary effects

Pulmonary adverse effects can be serious as a substantial mismatch in ventilation and perfusion is triggered by several factors. Alveolar derecruitment through absorption atelectasis can be widespread and commence quickly after initiation of hyperoxia by progressive washout of alveolar nitrogen and collapse of airways. Other hyperoxia-induced factors such as impaired mucociliary clearance and altered surfactant metabolism contribute to obstructive and adhesive atelectasis, respectively. In anaesthetised children, peri-operative hyperoxia decreases lung volume in the immediate postoperative period, accompanied by persistent ventilation inhomogeneity [19].

It can be suggested that lung volume lost due to resorption atelectasis caused by hyperoxia can be recruited by increasing positive end-expiratory pressure to 10 cm H_2O (0.98 kPa) or by the application of continuous positive airway pressure. However, several studies suggest that recruitment manoeuvres may have a detrimental effect on outcome [20]. Therefore, prevention of atelectasis by avoiding hyperoxia might avert the use of potentially harmful 'rescue' recruitment manoeuvres. Furthermore, pulmonary oedema may develop after prolonged exposure to hyperoxia when reactive oxygen species are formed and lead to a disturbed balance between oxygen-free radicals and oxygen scavengers (anti-oxidants) [21]. This imbalance contributes to oxidative stress which provokes mitochondrial damage, cellular dysfunction, altered microbial flora, ischaemia/reperfusion injury and local inflammation [22]. The vulnerability to oxidative stress is probably highly individual and potentially linked to underlying comorbidities.

Conclusion

The routine use of hyperoxia in all intubated surgical patients to prevent surgical site infections is not supported by convincing evidence. In contrast, accumulating evidence suggests a dose- and time-dependent relationship between hyperoxia and numerous significant complications. We believe that the administration of supraphysiological oxygen concentrations is an unnecessary intervention in the presence of adequate oxygenation.

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