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REVIEW ARTICLE

Perioperative hyperoxia: perhaps a malady in disguise

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Abstract

Oxygen is an element, which is used liberally during several medical procedures. The use of oxygen during perioperative care is a controversial issue. Anesthesiologists use oxygen to prevent hypoxemia during surgical procedures, but the effects of its liberal use can be harmful. Another argument for using high oxygen concentrations is to prevent surgical site infections by increasing oxygen levels at the incision site. Although inconclusive, literature concerning the use of high oxygen concentrations during anesthesia show that this approach may cause hemodynamic changes, altered microcirculation and increased oxidative stress. In intensive care it has been shown that high oxygen concentrations may be associated with increased mortality in certain patient populations such as post cardiac arrest patients. In this paper, a review of literature had been undertaken to warn anesthesiologists about the potential harmful effects of high oxygen concentrations.

Keywords: hyperoxia, oxidative stress, high oxygen concentrations, general anesthesia

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Introduction

Oxygen is an essential item in modern day medical armory and is amongst the most commonly used drugs in the clinical practice. Its delivery is a simple and effective intervention for acutely ill, especially hypoxemic, patients and most clinical professionals feel comfortable prescribing, and perhaps even overusing it [1, 2]. No guidelines for perioperative oxygen use exist. Other recent guidelines on oxygen supplementation recommend proper documentation of its use to allow future research and promote second thoughts as increasing evidence suggest inappropriate oxygen use can be harmful rather than purely beneficial [1]. We will review perioperative use of oxygen and the consequences of hyperoxia in surgical patients.

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Pathophysiology of high FiO_2

Fraction of inspired oxygen (FiO_2) is commonly titrated to peripheral capillary oxygen saturation (SpO_2) measured with pulse oximetry, which can detect hypoxemia but not hyperoxemia [3]. Although a SpO_2 level nearing 100% is intuitively reassuring to prevent risk of life-threatening hypoxemia, increasing FiO_2 blindly just to achieve that may have more detrimental effects [2, 4]. The primary goal of oxygen therapy is to increase oxygen available for aerobic metabolism, but it can also cause damage directly or via molecular sequelae of adverse metabolic alterations in perioperative period.

Circulatory effects of hyperoxia are complex. Hyperoxia causes systemic vasoconstriction and reduces microcirculation [5, 6]. Cardiac output and organ perfusion may become altered with high FiO_2 as heart rate drops, systemic vascular resistance rises and capillary permeability decreases [7]. Pulmonary circulation rises as a result of decreased pulmonary vascular resistance, but there is no confirmed subsequent benefit for the patient and this may even be accompanied by bronchoconstriction [8]. Cerebral vasoconstriction can reduce cerebral blood flow, which

can be beneficial or harmful depending on the context [9, 10]. These circulatory consequences may compromise tissue oxygenation contrary to an anticipated increase with a higher FiO_2, since tissue oxygenation depends on oxygen delivery to the tissues as well as oxygen content of blood.

Increasing FiO_2 is only one of the means of increasing arterial partial pressure of oxygen (PaO_2) and loading hemoglobin with oxygen (SpO_2). Together these factors determine oxygen content of the blood along with hemoglobin concentration. Increasing FiO_2 only marginally increases oxygen content of the blood when hemoglobin is adequately saturated as evident in the oxyhemoglobin disassociation curve [7]. In addition, a high FiO_2 leads to arterial accumulation of dissolved oxygen causing increased reactive oxygen species (ROS) formation. Superoxide, hydroxyl radicals and hydrogen peroxide are ROS formed for physiological purposes, but their excess causes cellular toxicity via increased lipid peroxidation, DNA damage and protein oxidation leading to organ dysfunction [7]. Innate anti-oxidative systems to protect against excess ROS exist; however, they easily become over-saturated and inadequate with increased oxidative stress. High perioperative FiO_2 has been shown to increase oxidative stress while limiting antioxidant response [11]. Tissues with high anabolic metabolism are especially prone to the oxidative damage by ROS [12].

Reactive oxygen species are key steps in the formation of bacteriotoxic metabolites such as hypochlorus acid and myeloperoxidases. Although a high FiO_2 may increase the ROS available for the host bactericidal defensive actions, it does not increase neutrophil's phagocytic activity or cytokine response [13]. Overall high FiO_2 impairs the immune systems' defensive mechanisms by causing actin damage compromising endothelium and macrophages [14, 15]. A high FiO_2 may contribute to the efficacy of antibiotics in preventing infections as many are oxygen-dependent in their effect [16]. Hyperoxia also leads to perturbation in elastin and collagen crosslinking and impairs mechanical aspects of tissue healing [17]. All these intricate and sometimes opposing factors form a complex relationship between FiO_2 and perioperative outcomes.

Clinical outcomes of high perioperative FiO_2

Studies of the pathophysiological outcomes of hyperoxia have been conducted in different animal models using variable oxygen levels, each under very specific conditions; therefore, generalization of their outcome and application to clinical practice is limited. Clinical trials to date have been difficult to compile in systemic reviews and meta-analyses to reach a single consensus on oxygen use, because in these studies control and intervention FiO_2, timing of the high FiO_2 intervention and primary outcome vary greatly and sufficient patient numbers are lacking [4].

Clinical consequences of high FiO_2 on the pulmonary system are now widely accepted. Directly, oxygen delivery increases only alveolar partial pressure of oxygen (PAO_2). When breathing higher than 80% oxygen, absorptive atelectasis results from the washout of nitrogen from the alveolar space, which then collapses as the remaining absorbable gases diffuse through the tissue [18, 19]. This atelectasis is also resistant to recruitment maneuvers [20], contributing to the observation that high intra-operative FiO_2 decreases end expiratory lung volume and PaO_2/FiO_2 ratio in surgical patients [11].

ROS formation in the airway also directly damages alveolar histology and impairs gas exchange [21]. Inhaling high FiO_2 can also result in tracheobronchitis leading to dyspnea and pleuritic chest pain in patients undergoing general anesthesia [22]. Chronic obstructive pulmonary disease patients suffer from increased airway inflammation and decreased hypoxic respiratory drive leading to hypercarbia on return to spontaneous inhalation [23]. Even during one lung ventilation, a lower FiO_2 adjusted according to PaO_2 may lead to a better outcome due to less inflammatory and oxidative injury [24]. A severe manifestation of lung damage can be seen in neonates ventilated with high FiO_2 as bronchopulmonary dysplasia (along with retinopathy and damage to the developing brain) as a result of inflammatory cascade involving increased ROS and decreased nitrous oxide production [25-27].

Surgical site infections (SSI) are the main causes of morbidity, mortality and increased cost of care amongst general surgical patients [28, 29]. Interventions to minimize the rate of these infections by optimizing blood flow and content have been focused mostly on surgical and patient-related factors; however, culprits related to anesthetic management, such as tissue perfusion, volume status, perioperative body temperature, blood transfusions and inspired oxygen concentration, have been investigated as well [30]. Adequate wound oxygen level is important for healing, but a rise in FiO_2 alone alters these levels insignificantly and therefore its local benefits may be overrun by the systemic harm over-oxygenation causes [8].

Studies of the clinical impact of high FiO_2's on the rate of SSI have shown inconsistent results. In one study amongst general surgical patients, exposure to high FiO_2 during operations for about 200 minutes, and for 2 hours post-operatively resulted in higher infection rates and longer hospitalization [31]. Another trial found better anastomotic healing rates post-total gastrectomy

when patients were ventilated with higher FiO_2 during and for 6 hours after the operation [32]. On the other hand, Mayzler et al. observed no difference in the rates of surgical site infections during colorectal operations performed with either 30% or 80% oxygen [33]. Such conflicting results are numerous due to the great variation in the study designs as in these two examples. Meta-analysis of current literature with surgical site infection rate as primary outcome concludes no overall benefit of high FiO_2 (except for a potential benefit for certain subgroups, i.e. if prophylactic antibiotics were used) and suggests even a potential harm [4].

During coronary artery bypass surgery, use of a high FiO_2 to obtain hyperoxemia does not offer any benefits over lower FiO_2's with normal arterial oxygen levels in terms of degree of myocardial damage and mortality outcome [6]. A high FiO_2 decreases gas microembolism formation in the cardiopulmonary bypass, but whether this translates into a clinical benefit is unclear [34]. Pre-conditioning the healthy heart to hyperoxia before a cardiopulmonary bypass may improve outcomes after a transient global ischemia. However, this is likely due to increased anti-oxidant mechanisms from pre-conditioning [6]. Hyperoxia has been shown to increase infarct size and mortality after myocardial ischemia and cerebral infarct as well [10, 35].

Postoperative nausea and vomiting (PONV) is a common complication in perioperative period and several factors contribute to its development. Reduction of PONV has been observed in patients undergoing colorectal surgery with high FiO_2 [36]; however, overall consensus from meta-analyses conclude that effect of FiO_2 on PONV is minimal and there is not sufficient evidence to promote its use as a prophylactic measure [8].

Due to its potential harm, oxygen should be used carefully in post-operative and critical care areas as well. Based on current evidence, post-operative oxygen therapy should aim SpO_2 levels of 88- 94% for preterm neonates, 95% for infants, above 95% for children and elderly, above 98% for adults and between 88-92% for COPD patients in order to achieve the minimum risk/benefit ratio [8]. Comprehensive clinical data to reach a consensus on whether hyperoxia affects the outcomes of critically ill patients remains insufficient. A meta-analysis only concludes that hyperoxia is associated with a greater mortality in mechanically ventilated post-cardiac arrest and stroke and traumatic injury subset of general ICU patients [37].

Conclusion

In summary, oxygen is an essential drug for treating or preventing hypoxemia perioperatively. The harm caused by excess FiO_2 is almost always iatrogenic and can be prevented with careful use of oxygen. A recent review of current literature concludes that strong clinical evidence is insufficient for showing the benefit of high perioperative FiO_2 and warns off its routine use due its potential detrimental effects [2, 4, 36]. Apart from solely increasing FiO_2, tissue oxygenation can be improved by ensuring adequate alveolar ventilation, improved diffusion capacity of the lung, sufficient hemoglobin level and optimal metabolic status [1]. More goal and context specific randomized clinical trials using standard protocols are required to reach a better understanding.

Conflict of interest

Nothing to declare

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