Hyperoxia and Oxidative Stress in Anesthesia and Critical Care Medicine

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**ABSTRACT**

Oxygen administration is particularly relevant in patients undergoing surgery under general anesthesia and in those who suffer from acute or critical illness. Nevertheless, excess $O_2$, or hyperoxia, is also known to be harmful. Toxicity arises from the enhanced formation of Reactive Oxygen Species (ROS) that, exceeding the antioxidant defense, may generate oxidative stress. Oxidative stress markers are used to quantify ROS toxicity in clinical and non-clinical settings and represent a promising tool to assess the optimal $FiO_2$ in anesthesia and critical care setting. Despite controversial, the guidelines for the regulation of $FiO_2$ in such settings suggest the adoption of high perioperative oxygen levels. However, hyperoxia has also been shown to be an independent mortality risk factor in critically ill patients.

In this literature review, we discuss the biochemical mechanisms behind oxidative stress and the available biomarkers for assessing the pro-oxidant vs antioxidant status. Then, we summarize recent knowledge on the hyperoxia-related consequences in the most common anesthesia and critical care settings, such as traumatic brain injury or cardiac arrest. To this purpose, we searched the Pubmed database according to the following combination of key words: ("hyperoxia" OR "$FiO_2$" OR "oxygen therapy") AND ("oxidative stress" OR "ROS" OR "RNS" OR "lipid peroxidation") AND ("anesthesia" OR "surgery" OR "intensive care"). We focused in the results from the past 20 years. Available evidence points toward a conservative monitoring and use of oxygen, unless there is solid proof of its efficacy.

Key words: Hyperoxia, Oxidative Stress, Anesthesia, Critical Care, Oxygen

## Introduction

Molecular oxygen ($O_2$), a common drug and an essential component of the body, functions as the last acceptor of electrons in the major catabolic process that converts the biochemical energy contained in nutrients into high-energy adenosine triphosphate. $O_2$ is currently the most prescribed drug among hospitalized patients [1]. $O_2$ therapeutic properties have been applied since 1798, when Thomas Beddoes, the pioneer of respiratory therapy, opened the Pneumatic Institute where both $O_2$ and nitrous oxide were used to treat asthma and congestive heart failure[2]. $O_2$ administration counterbalances morbid conditions where its delivery or utilization is impaired. $O_2$ administration is particularly relevant in patients undergoing surgery under general anesthesia and in those who suffer from acute or critical illness. High $O_2$ inspired fraction ($FiO_2$) is applied before intubation and upon awakening in the operatory room when anesthesia-related complications are most likely to happen[3]. In critically ill patents, high $FiO_2$ is a cornerstone treatment to sustain cell function against processes leading to tissue hypoxia and eventually cell death. Supplemental $O_2$ therapy may also lead to excess blood $O_2$ levels, a condition called hyperoxemia. As a $PaO_2$ range of 80–100 mmHg is generally used to define a normal arterial blood $O_2$ concentration in individuals breathing room air at sea level, any $PaO_2$ value> 100 mmHg may be considered as hyperoxemia[4] even if this definition varies among authors. Among the systemic effects of hyperoxemia, a most notable one is linked to the generation of oxidative stress[1].

Oxidative stress is the product of the imbalance between the production of Reactive Oxygen Species (ROS) and the organism's ability to inactivate them. Although several biochemical markers for measuring oxidative stress are now available by means of complex laboratory procedures, they are not yet available at the bedside, yet they may help exploring the impact of oxidative processes in critically ill patients as well as in the perioperative period.

The purpose of this narrative review is to recapitulate the biochemical basis of hyperoxia-induced oxidative stress, to discuss the available biomarkers for measuring oxidative stress and to summarize the recent knowledge about the hyperoxemia-related consequences related to the field of perioperative medicine, critical care and acute illness. To this purpose, we searched the Pubmed database (journals in English) according to the following parameters: ("hyperoxia" OR "$fiO_2$" OR "oxygen therapy") AND ("oxidative stress" OR "ROS" OR "RNS" OR "lipid peroxidation") AND ("anesthesia" OR "surgery" OR "intensive care"). Remarkably, only 194 published issues concern all three analyzed keywords. The Venn diagram[5] of the outcomes of this search is shown in figure 1. This review is focused into data related to clinical settings in adult human patients. First, we will

discuss the use of oxidative stress markers in several studies aimed at demonstrating the biochemical effects of hyperoxemia, as listed in Table I. Then we will explore the clinical consequences of hyperoxia, according to the studies listed in Table II. The aim of this review article is to highlight the fundamental role of oxidative stress as the main molecular mechanism through which $O_2$ exerts its toxic effects, especially in clinical contexts related to intensive care medicine and anesthesia. In perspective, this study should contribute to the identification of a panel of easily measurable markers that may prove suitable to monitor and optimize $O_2$ therapy.

**Oxidative stress, a mechanism beyond oxygen toxicity**

It is recognized that excess $O_2$ increases the oxidative stress through at least three pathways.

- Increased rate of ROS production as a result of excess fueling of the respiratory chain and mitochondrial uncoupling.
- Increased formation of Reactive Nitrogen Species (RNS) from the reaction of ROS with NO and production of dangerous short-living species.
- Lipid peroxidation, that compromises the cell membrane stability and hence functionality.

Oxidative stress leads to damage of molecular and supra-molecular structures and hence to systemic diseases. However, this situation also activates anti-oxidant defense mechanisms through a positive feedback aimed at compensating ROS reactivity, at detoxifying pro-oxidants and at repairing damage[5]. Unbalanced oxidative stress may cause phenomena linked to the oxidation of DNA, proteins and cell membrane lipids.

*Reactive Oxygen Species*

In normal conditions, $O_2$ is reduced to water in the mitochondrial inner membrane, but 0.1–2% of the electrons along the oxidative phosphorylation process are diverted to generate superoxide anion ($\bullet O_2^-$) [6], which gives rise to hydrogen peroxide ($H_2O_2$), singlet oxygen ($^1O_2$), hydroxyl radical ($\bullet OH$), collectively known as reactive $O_2$ species (ROS). Any increase in $O_2$ availability leads to increase ROS (figure 2).

Various biochemical markers are used to evaluate ROS production. Great effort has been made in the past to identify an array of such markers (Table I). The most relevant are hydroperoxides, which can be assessed by the derivative of the Reactive Oxygen Metabolites (d-ROM) test. Such

compounds are the early results of the interaction of ROS with organic molecules and can be easily detected in patients' plasma. However, when assessed in plasma from adult patients undergoing surgery while exposed to $FiO_2$=0.5, this method did not show any significant hyperoxia-related oxidative stress.[7] Other significant markers are Highly Reactive Oxygen Species (hROS), indirectly assessed by a fluorometric assay (hROS test). This marker was useful in showing an increased oxidative stress in critically ill patients undergoing hyperoxemic mechanical ventilation.

*Reactive Nitrogen Species*

$O_2^{-}$• reacts with nitric oxide (NO) to generate peroxynitrite ($ONOO^-$), the best known reactive nitrogen species (RNS). This reaction reduces NO availability in the endothelium, which in turn reduces local vasodilation. This causes hyperoxic vasoconstriction, a phenomenon well described in healthy volunteers and congestive heart failure patients[9]. $ONOO^-$ and its conjugated acid, peroxynitrous acid (ONOOH), are highly reactive species that react with heme-containing proteins as hemoglobin[10], lipids, some aminoacid residues, DNA bases and low-molecular weight antioxidants[11].

The most relevant marker to estimate NO and RNS is the level of nitrites and nitrates (NOx), proportional to NO plasma levels [12]. NOx can be measured by reacting the colorless solution containing nitrite with the Griess reagent, that converts nitrites in a purple/pink dye [13]. To obtain a measure of total NOx by this reaction, which involves only nitrites, nitrates are reduced into nitrites by either an enzymatic or a chemical method. NOx can be a promising marker for assessing the harmful effects of hyperoxia. In fact, a significant decrease in NOx was observed in healthy volunteers after breathing at $FiO_2$=1.0 for 30 minutes [14]. The value of NOx is also upregulated in patients with primary episodes of septic shock, despite a potential increased production of RNS[15]. Decreased NOx is considered a cardiovascular risk factor because of the vasodilatation impairment [16].

*Lipid peroxidation*

Lipids, the main constituents of the cell membranes, are susceptible to peroxidation when in contact with ROS. As phospholipids play a major role in preserving the outer membrane architecture, their peroxidation causes fluidity changes that may influence receptors function and trigger inflammatory or apoptotic pathways [17]. The inner mitochondrial membrane structure is also sensitive to the oxidative stress due to the presence of cristae that are essential for the efficiency of oxidative phosphorylation.

Lipid peroxidation can be assessed through the biomarker malondialdehyde (MDA), a major product of lipid peroxidation that can be easily measured in plasma [18] by the chemical methods listed in the second section of table I. Several studies have shown the potential uses of this marker in the anesthesia and intensive care setting. MDA is increased in critically ill patients, with respect to healthy subjects[19]. Increased MDA plasma levels have been observed in healthy volunteers exposed to $FiO_2$=1.0 [14, 20, 21]. Such increase was also an early effect of colorectal surgery, in which patients are exposed to supplemental oxygen[22]. Nevertheless, in that study, no significant differences in MDA were observed between $FiO_2$=0.8 and $FiO_2$=0.4.

*Antioxidant defense*

Antioxidants are the most effective and convenient approach to control the damage derived from oxidative stress. Preventive antioxidants interfere with the initiation process by blocking the formation of free radicals[23]. Superoxide dismutase (SOD), gIutathione peroxidase (Gpx) and catalase (CAT) attack hydroperoxides and $H_2O_2$ (figure 2). Antioxidants may also act as chain-breaking, radical-trapping substances, by reacting with ROS more rapidly than ROS attack the oxidizable substrate. As a result, the products of such reaction don't propagate the autoxidation chain reaction. A few of these antioxidants, such as phenols and polyphenols, are exogenous and they are introduced as food or dietary supplements, or are prescribed as antioxidant drugs.

The most common methods to evaluate the antioxidant response to oxidative stress are based on the direct assessment of some of the endogenous antioxidants, especially SOD, Gpx and CAT. Such methods were used to evaluate the effects of hyperoxia in both healthy volunteers and general anesthesia patients. Plasma levels of SOD are higher, at the end of laparoscopic surgery, in patients treated with intraoperative $FiO_2$=0.8, when compared to the those treated with $FiO_2$=0.4 [22]. In alternative, the antioxidant capacity can be assessed indirectly by measuring the ability to oppose the pro-oxidant action of a standard reagent, as in the Ferric Reducing Ability of Plasma (FRAP) and in the Total Antioxidant Capacity (TAC) tests. The antioxidant capacity, measured by the FRAP test, in patients undergoing colorectal surgery is decreased after intraoperative exposure to $FiO_2$=0.5 [7]. A similar result was obtained by the TAC test in pediatric patients undergoing laparoscopic surgery with $FiO_2$=0.5 [24].

**Supplemental $O_2$ therapy and hyperoxia in the perioperative period**

Deliberately high supplemental $O_2$ is administered while inducing anesthesia and before extubating to grant continuous oxygenation in the event of problematic airways management[25]. Such practice is

strongly encouraged by influential recent guidelines[26, 27]. The 2016 WHO guidelines for $O_2$ administration practice emphasized the important role of pre-oxygenation at $FiO_2$=1.0 before induction, with the subsequent maintenance of high $FiO_2$ up to six hours after surgery in order to significantly reduce surgical site infection incidence[28].

From a strictly physiological point of view, increasing $FiO_2$ from 0.21 to 1.0 produces a five-fold increase in dissolved $O_2$, despite a mere 13% increase in the total blood $O_2$ content. In fact, when healthy subjects with arterial $O_2$ saturation in the 95–100% range breathe at $FiO_2$>0.21, the amount of $O_2$ physically dissolved in plasma increases linearly with $FiO_2$, but the amount of $O_2$ bound to hemoglobin does not vary considerably because hemoglobin is already almost fully saturated with $O_2$. This picture, however, may change in patients undergoing intubation or extubation, which necessarily imply a short apnea. During apnea, circulating hemoglobin binds the $O_2$ contained in the alveoli, a rather limited $O_2$ store. With a normal functional residual capacity, apnea tolerance is <1 min, after which the arterial $O_2$ saturation decreases by 30%/min at $VO_2$=250 ml/min$^{-1}$. Thus, breathing hyperoxic mixtures just prior to intubation or extubation may lead to a several-fold improvement of apnea tolerance, thereby considerably reducing the risk of hypoxemia.

The strength of the recommendation supporting the administration of high $FiO_2$ in the operative and post-operative periods was recently criticized[29]. A large randomized trial not only did not report any benefit, such as a decreased incidence of surgical site infections, but also reported a higher mortality in patients treated with $FiO_2$=0.8 after follow-up[30]. Two recent metanalysis on the use of high preoperative $FiO_2$ came to the conclusion that there is no evidence of harm regarding the use of perioperative high $FiO_2$, although its benefit, initially thought toward the general population, is restricted to surgical patients undergoing general anesthesia with tracheal intubation [31, 32]. Supplemental $O_2$ therapy was long believed to diminish the risk of postoperative nausea and vomit (PONV) through unknown mechanisms. However, it has been shown that the onset of PONV might be related to diminished levels of nitrous oxide rather than increased levels of $O_2$[33].

If supplemental $O_2$ offers uncertain advantage in the perioperative care of patients, it might cause a number of harmful effects such as the formation of ROS toxicity and atelectasis. In fact, high perioperative $FiO_2$ fuels ROS production and oxidative stress and a more direct exposure to high $FiO_2$ can strongly affect the metabolism of lungs cells, by decreasing their $O_2$ consumption rate [34]. High $FiO_2$ in mechanically ventilated patients may result in reabsorption atelectasis[35]. Lung parenchyma atelectasis depresses the respiratory function by augmenting the shunt fraction. Contradicting this evidence, a trial investigating the relationship between high $FiO_2$ and

postoperative atelectasis did not find any difference in radiologic imaging suggesting atelectasis, when comparing $FiO_2$=1.0 and $FiO_2$=0.3[36] ventilated patients. In terms of patient-oriented outcome, the rate of postoperative respiratory complications was not different in surgical patients treated with intraoperative $FiO_2$=0.8 with respect to $FiO_2$=0.4 group according to a sub-analysis of a large trial involving more than 5000 patients[37]. Based on these data, although being a suspected mechanism of pulmonary complications, there is no definitive evidence of hyperoxemia affecting atelectasis, thereby causing respiratory postoperative complications and in turn worsening patients outcome.

**Hyperoxia in ICU and mechanically ventilated patients**

Critically ill patients are more likely to be exposed to high $FiO_2$ due to the underlying disease often impairing blood oxygenation and organ perfusion. The hypothesis that hyperoxia could be detrimental for ICU and mechanically ventilated patients has attracted attention from researchers who face the challenge of dissecting true harmful effects of hyperoxia from its significance as a marker of illness severity. The risk of hyperoxic acute lung injury increases after breathing $FIO_2$>0.7 for an extended period of time[38]. Evidence from experimental studies were initially supported by a retrospective analysis of data extracted from a large databases of critically ill patients from the Netherlands. According to this study, both high and low $PaO_2$ in the first 24 hours after ICU admittance were associated with higher mortality, resulting in a U-shaped relationship between $PaO_2$ and patients' outcome[39]. A later larger observational study from Australia and New Zealand (examining data from more than 150,000 patients) found an association between early hypoxia, but not hyperoxia, and mortality in ICU patients, concluding that any harmful effect of hyperoxia in this group remains to be proven[40]. In order to assess the possibility of a lower oxygen therapy threshold ($SpO_2$ target 88-92%) compared to a more liberal approach ($SpO_2$ target 96%) an exploratory trial found that the more conservative strategy was feasible without significant differences regarding the safety outcome and in turn this approach potentially lead to a reduced exposure to hyperoxia[41]. The oxygen-ICU randomized trial compared a conservative oxygenation strategy ($SpO_2$ 94 to 98%) with a conventional strategy ($SpO_2$ 97 to 100%) among patients with predicted length of stay longer than 72 hours[42]. Data from this study showed an absolute risk reduction for intensive care unit mortality of 8.6% in the conservative strategy group. According to the authors a possible explanation of the negative effect of hyperoxia includes a higher ROS generation although specific measurements were not carried out in that population. Most notably the HYPERS2S trial investigated the effect of $FiO_2$= 1.0 compared to a 88-95% $SpO_2$-targeted oxygenation in the first 24 hours in ICU patients with septic shock[43]. 28-day mortality was higher in the high $FiO_2$ group and so was the incidence of ICU-acquired weakness and atelectasis. An

association between hyperoxia and pulmonary complications in ICU was suggested also by an increase in diagnosis of ventilator associated pneumonia in patients with $PaO_2$ >120 mmHg for longer period of time[44]. In the recent years a composite bulk of evidence made of retrospective studies and randomized trials in critically ill patients has emerged raising concern over the adoption of liberal oxygenation strategies in favor of more conservative approaches.

*Traumatic Brain Injury*

In head-injured patients, brief periods of hyperoxia with $FiO_2$=1.0 were demonstrated to reduce intracranial pressure and to improve both brain tissue $PO_2$ and jugular venous oxygen saturation [45]. In a retrospective analysis on data extracted from more than 3,000 patients, the outcome measured as difference between actual and predicted survival in TBI patients with $PO_2$ ranging from 110 to 487 mmHg was better than that of hypoxic or extremely hyperoxic patients[46]. These results were corroborated by another cohort study showing an improved survival among TBI patients in the 250-486 mmHg $PO_2$ range measured in the first 72 hours[47]. In a long-term outcome analysis, hyperoxia defined as $PO_2$>100 mmHg did not appear to negatively affect mortality at 6 months after TBI[48]. Also, a post-hoc analysis of the Brain-Hypothermia Study addressing the use of hyperoxia in TBI found significantly higher survival rates and better outcomes among patients with the higher $PO_2$[49]. Of note, both survivors/good outcome and non survivors/unfavorable outcome showed average $PO_2$ values above 100 mmHg. Recent data from over 24,000 TBI patients suggested a direct association between in-hospital mortality and hypoxia but not hyperoxia[50]. On the contrary Brenner et al. found an association between both early hypoxemia and hyperoxemia (>200 mmHg) and short-term mortality in their cohort of patients. The same results came from a study by Rincon et al. where early hyperoxia ($PO_2$>300 mmHg) resulted in higher risk of death (Odd Ratio 1.5) compared to the normoxia group. In order to clarify possible mechanisms beyond hyperoxia toxicity, Quintard et al. divided a cohort of TBI patients, whose brain $PO_2$ was monitored with microdialysis techniques, based on ranges of administered $FiO_2$[51]. They found an association between the concentration of excitotoxic neurotransmitter glutamate and incremental $FIO_2$ levels. In this context, $PO_2$> 150 mmHg was associated with the highest glutamate concentrations.

Results from recent trials leave the question of hyperoxia in TBI open. If hyperoxia may confer a benefit in this group of patients, contradictory pieces of evidence advocate for a tight oxygenation monitoring in neurocritical care and further larger studies are needed to understand its role in TBI.

*Stroke*

As for TBI, supplemental $O_2$ administration in stroke is supposed to sustain tissue metabolism under hypoxemic conditions although this may fuel ROS-triggered, potentially cytotoxic secondary brain damage. Since brain tissue hypoxia plays a critical role in stroke, $O_2$ therapy is still considered a mainstay of supportive care in brain ischemia to maintain $SpO_2$>94% despite limited data from clinical trials[52]. Among non-intubated patients, supplemental low-flow $O_2$ did not improve neither mortality nor disability in patients with minor or moderate stroke[53]. However, a small trial showed that in selected patients with acute stroke and MRI signs of perfusion-diffusion mismatch, early high-flow oxygen therapy transiently reduced clinical deficits and radiological abnormalities without positively affecting long-term outcome[54].

A retrospective multicenter cohort study investigated the outcome of stroke patients undergoing mechanically ventilation admitted to ICU[55]. The authors divided patients according to $PO_2$ values in the first 24 hours in three groups: hypoxia ($PO_2$<60 mmHg), normoxia (60-300 mmHg) and hyperoxia ($PO_2$>300 mmHg). Mechanically ventilated patients with brain ischemia whose treatment resulted in hyperoxemia showed significant higher mortality compared to either normoxic or hypoxic patients.

Also according to a recent large multicenter trial, prophylactic low-flow supplemental $O_2$ in normoxic stroke patients did not reduce mortality, neither it improved neurological outcome as measured with the Rankin Scale at 90 days[56]. These recent findings do not support the administration of prophylactic oxygen in the stroke setting. A large prospective study on effects of hyperoxemia in mechanically ventilated patients has not been conducted yet.

*Myocardial infarction*

One of the most widely administered therapeutic tools in patients with suspected myocardial infarction (MI) is supplemental $O_2$. This practice is not usually relegated just to patients with MI and hypoxia but to most patients in the hypothesis that supplying more $O_2$ to the ischemic myocardium might reduce the size of the infarction. Nevertheless, high $FiO_2$ in ischemic heart disease setting can prompt reduction of blood flow velocity and increase coronary resistance[57]. Modifications are quickly reverted by administration of Vitamin C, a potent antioxidant which is thought to quench oxygen-induced ROS. Supporting such hemodynamic effect, high-flow $O_2$ induced impairment in diastolic relaxation and increased left ventricular filling pressure in congestive heart failure patients[58]. Physiological evidence was confirmed by a retrospective analysis of patients admitted to the emergency department with MI showed an increased 28-day mortality among patients with demonstrated hyperoxia, here defined as $PO_2$>180 mmHg[59]. In 2016, a

metanalysis considering randomized trials on $O_2$ supplementation and MI concluded that given the limited amount of evidence, the effect of $O_2$ on mortality and its safety was uncertain, advocating for more trials addressing the question[60]. Lately, in the Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction clinical trial, the authors randomized more than 600 subjects with prehospital evidence of myocardial infarction at the EKG either to ambient air or oxygen delivered with face mask at 8 L/min[61]. The $O_2$-treated group had higher increase in Creatine Kinase level at the time of infarction and larger infarct size area as showed with a 6 months follow-up Cardiac Magnetic Resonance. The more recent DETO$_2$X-SWEDEHEART study looked at results coming from more than 6000 non-hypoxic patients with suspected MI randomized to oxygen via face mask or ambient air for 6 to 12 hours[62]. Mortality for any cause within 1 year and risk of re-infarction did not differ between oxygen and air group. Current clinical practice guidelines do not incorporate results from latest studies yet but, with limited evidence supporting oxygen use in normoxic MI patients, suggest withholding its administration[63].

*Cardiac arrest*

Sudden cessation of functioning of the heart can severely impair $O_2$ delivery to tissues and result in cell death. For this reason, higher $PO_2$ levels during the time of the arrest are associated with increased possibility of discharge from hospital[64]. Patients who suffer from cardiac arrest and are successfully resuscitated, may present a condition called post-resuscitation (post-ROSC) syndrome, which encompasses myocardial, brain and multi-organ failure [65]. Hyperoxia has a vasoconstrictor effect on the cerebral vessels and it may worsen the oxidative stress-induced damage after reperfusion. This physiological background has been the foundation of research looking at the association between hyperoxia and outcome after return of spontaneous circulation in cardiac arrest. Two large retrospective studies conducted in US and Australia and New Zealand reported a higher risk of death among patients resuscitated from cardiac arrest and exposed to hyperoxemia [66, 67]. The first, a cohort study considering more than 6000 patients, examined three groups, hyperoxemia ($PO_2$>300 mmHg), normoxemia and hypoxemia ($PO_2$<60 mmHg), comparing oxygenation levels post resuscitation after cardiac arrest. In this study patients in the hyperoxemia group had higher in-hospital mortality at 28 days when compared to patients in the normoxia group. The second study reported an analysis conducted on data from 125 centers and more than 12,000 patients. Oxygenation thresholds for analysis of subgroups were the same as the first. Hyperoxia, initially showing the highest mortality level, was not consistently associated with mortality once the analysis was corrected to account for potential confounders. Ethical and practical reasons make it difficult to perform large randomized trials comparing different levels of oxygenation in the field of cardiac

arrest. However, a human randomized controlled trial compared the effects of two groups of post-ROSC patients given $FiO_2$=0.3 and $FiO_2$=1.0 **[68].** The results of the study did not show any difference in survival because the study was underpowered for exploring this outcome. Focusing on surrogate outcomes, subgroup analysis showed that $FiO_2$=1.0 was associated with an increased level of neuron-specific enolase, a circulating marker of neuronal injury. A metanalysis of observational studies on the role of hyperoxemia after cardiac arrest resuscitation demonstrated a higher in-hospital mortality in patients with hyperoxemia[69]. The authors concluded that since high $PO_2$ has no detectable benefit in this group, supplemental $O_2$ therapy has to be managed cautiously. To strengthen this critical issue, a metanalysis examining studies performed in various categories of ICU patients revealed higher mortality rate in patients exposed to hyperoxia compared to normoxia, especially following cardiac arrest and extracorporeal life support[70]. Providing high $O_2$ during cardiopulmonary resuscitation seems reasonable but once reperfusion has been accomplished, $O_2$ levels need to be carefully monitored and appropriately adjusted. Indeed, there is still no experimental support to the view that $O_2$ supplementation increases $O_2$ delivery. By contrast, several studies report decreased cardiac output and increased systemic vascular resistance in response to hyperoxia[71].

**Limits of the study**

The selection of the keywords used for the literature search has obviously a great impact on the database employed to perform the review. For example, the same search as that described above performed without quoting the terms gave 2825 instead of 194 hits but was judged to be rather unspecific. In order to ascertain the focus in this review, the search system reported above was checked against other searches and refined to yield the optimal results.

The issues related to hyperoxemia impact virtually all clinical fields, but perhaps two of them are the most relevant. First, cardiac surgery, where increased arterial oxygenation may not correspond to changes in oxygen handling[72]. In facts, hyperoxemia is expected to lead to vasoconstriction and mitochondrial dysfunction, likely with relevant myocardial derangement[73]. Second, extracorporeal membrane oxygenation, where hyperoxemia is associated with fewer episodes of gaseous micro-embolism (but the most recent models of membrane oxygenator have reduced the incidence this risk). On the other hand, hyperoxemia may also lead to postoperative cognitive impairment[74], that is partially compensated by hyperoxic cerebral pre-conditioning[75]. Although these are very important issues to be considered in the future, in this review we focus into the clinical contexts related to intensive care medicine and anesthesia.

## Conclusions

In acute and perioperative care settings the gap between organ $O_2$ requirement and supply is often filled with supplemental $O_2$ therapy which may increase $PO_2$ and create hyperoxemia. Although additional oxygen is a cornerstone of medical management under stressful conditions, it fuels the generation of ROS thereby inducing harmful oxidative stress. According to this line of argument, surrogate endpoints such as the oxidative stress markers were described as a potential useful resource for evaluating the effects of $O_2$ treatment.

A renovated interest in understanding important consequences of high $O_2$ treatment has led to important contributions by large clinical trials over the last few years. Guidelines and metanalysis agree on safety and efficacy of the adoption of high $FiO_2$ in intubated patients undergoing general anesthesia. On the opposite side, in critically ill mechanically ventilated patients a conservative $O_2$ therapy approach has been advocated while in myocardial infarction and stroke recent evidence suggest that $O_2$ may negatively affect outcome or at least confer no advantage in normoxemic patients. Although extensive trials and a better knowledge of the underlying molecular and cellular mechanisms are still warranted for establishing role of hyperoxemia in TBI and cardiac arrest, available evidence points toward a conservative monitoring and use of $O_2$ apart from clinical fields in which there is solid proof of its efficacy.

## KEY MESSAGES

- Hyperoxia, or excess $O_2$, is a common condition in patients undergoing surgery under general anesthesia and in those who suffer from acute or critical illness.

- As hyperoxia is known to enhance the formation of Reactive Oxygen Species, it may be harmful.

- The effects of hyperoxia on morbidity and mortality are still under evaluation in several anesthesia and intensive care settings.

- Surrogate endpoints, such as the measurement of oxidative stress markers, can be a useful resource for evaluating the effects of $O_2$ treatment in a case-by-case way.

**List of abbreviations**

| | |
|---|---|
| $\bullet O_2^-$ | Superoxide anion |
| •OH | Hydroxyl radical |
| CAT | Catalase |
| CNS | Central nervous system |
| $FiO_2$ | Fraction of inspired oxygen |
| FRAP | Ferric reducing ability of plasma |
| GPx | Glutathione peroxidase |
| hROS | Highly Reactive Oxygen Species |
| ICU | Intensive Care Unit |
| MDA | Malondialdehyde |
| NOx | Nitrites and nitrates |
| $O_2$ | Oxygen |
| $PaO_2$ | Arterial partial pressure of oxygen |
| $PO_2$ | Partial pressure of oxygen |
| RNS | Reactive nitrogen species |
| ROS | Reactive oxygen species |
| ROSC | Return of spontaneous circulation |
| SOD | Superoxide dismutase |
| $SpO_2$ | Peripheral saturation of oxygen |
| TBI | Traumatic brain injury |

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**TABLE I.** Main plasma oxidative stress markers and their relative change upon exposure to hyperoxia (if P<0.05). NS=not significant.

| **Study** | **Marker** | **Assay** | **Model** | **Time, min** | **$FiO_2$** | **% change** |
|---|---|---|---|---|---|---|
| Tsuchiya[7] | Hydroperoxides | d-ROMs | Surgery patients | 120 | 0.5 | NS |
| Donati[8] | hROS | Hydroxyphenyl fluorescein | ICU patients | 120 | 1.0 | +11% |
| Loiseaux-Meunier[21] | MDA | HPLC-MS | Healthy volunteers | 125 | 1.0 | +14% |
| Modun[14] | MDA | HPLC-MS | Healthy volunteers | 30 | 1.0 | +30% |
| Brerro-Saby[20] | MDA + MDA-like products | TBARS | Healthy volunteers | 50 | 1.0 | +20 |
| Koksal[22] | MDA + MDA like products | TBARS | Surgery patients | 200 | 0.8 | +38% |
| | | | | | 0.4 | +31% |
| Koksal[22] | SOD | Enzymatic assay | Surgery patients | 200 | 0.8 | +60% |
| Tsuchiya[7] | Antioxidant capacity | FRAP | Surgery patients | 120 | 0.5 | -14% |

**Table II**. Summary of the most recent randomized trial investigating hyperoxia in perioperative and critical care medicine.

| Study | Study design (n=subjects) | Subjects | Oxygen therapy | Randomization time | Primary endpoint | Effects of hyperoxia |
|---|---|---|---|---|---|---|
| Girardis[42] | Open-label (n=434) | Critically ill | $PaO_2$=70-100 mmHg vs $PaO_2$>150 mm | ≥72 h | Mortality | Higher mortality |
| Hofman[62] | Open-label, registry-based (n=6629) | Suspected myocardial infarction patients | $FiO_2$= 0.21 vs 6 l/min $O_2$ | 11.6 h | Death from any cause within 1 year | No benefits |
| Koksal[22] | Single-blind (n=40) | Colon cancer surgery patients | $FiO_2$=0.80 vs $FiO_2$=0.40 | 200 min | Oxidative stress markers, arterial blood gas data | Decreased tidal volumes, $PaO_2/FiO_2$ ratio, and increased lactate levels and oxidative stress |
| Kuisma[68] | Pilot study (n=28) | Post-resuscitation patients | $FiO_2$=0.3 vs $FiO_2$=1.00 | 1 h | Neuron-specific enolase | Increased level of neuron specific enolase at 24h |
| Meyhoff[30] | Double blind (n=1400) | Laparotomy patients | $FiO_2$=0.8 vs $FiO_2$=0.3 | During and for 2 h after surgery | SSI | No difference in risk of SSI |
| Roffe[56] | Single-blind (n=8003) | Stroke patients | $FiO_2$=0.21 vs continuous 2-3 l/min $O_2$ vs nocturnal 2-3 l/min $O_2$ | 72 h | Disability | No benefits in the following 3 months |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ronning[53] | Open-label (n=550) | Stroke patients | $FiO_2$=0.21 vs 3l/min $O_2$ | 24 h | 1-year survival, neurological impairment and disability | No benefits |
| Stub[61] | (n=441) | Myocardial infarction patients | $FiO_2$=0.21vs 8 l/min $O_2$ | 150 min | Infarct size, cardiac enzymes, troponin I, and creatine kinase | Increase in early myocardial injury and larger myocardial infarct size at 6 months |

## LEGENDS OF FIGURES

Figure 1. Venn diagram for the following search strategy: "(anesthesia OR intensive care OR surgery OR critically ill) AND (hyperoxia OR oxygen therapy OR high $FiO_2$ OR hyperoxic) AND (oxidative stress OR lipid peroxidation OR ROS OR RNS)". *White filled circle*: results of the search "anesthesia OR intensive care OR surgery OR critically ill". *Yellow filled circle*: results of search for "hyperoxia OR oxygen therapy OR high $FiO_2$ OR hyperoxic". *Blue filled circle*: results of the search for "oxidative stress OR lipid peroxidation OR ROS OR RNS". *Red intersection area*: results of the search for "(anesthesia OR intensive care OR surgery OR critically ill) AND (hyperoxia OR oxygen therapy OR high $FiO_2$ OR hyperoxic) AND (oxidative stress OR lipid peroxidation OR ROS OR RNS)". *n*: number of published issues

Figure 2. Effects of excess molecular $O_2$ on ROS production. Excess $O_2$ is turned into the radicals $O_2$•- and HO•. HO• can cause damage especially to the plasmatic membrane through lipid peroxidation, which can be assessed by measuring the marker MDA. ROS increase also activates the antioxidant defenses: while SOD catalyzes the production of the less reactive ROS $H_2O_2$ from the radical $O_2$•-, GPx and CAT turn $H_2O_2$ into water. Eccess •$O_2$- reacts with NO to produce ONOO-, therefore reducing NO pool and increasing oxidative stress. *GPx*: glutathione peroxidase; *MDA*: malondialdehyde; *SOD*: superoxide dismutase; *NO*•: Nitric Oxide; *ONOO-*: peroxynitrite. *Red arrows*: oxidative stress-related damages. *Blue arrows*: antioxidant mechanisms.