The effects of oxygen in critical illness

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2

BENCH-TO-BEDSIDE REVIEW: THE EFFECTS OF HYPEROXIA DURING CRITICAL ILLNESS

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ABSTRACT

Oxygen administration is uniformly used in emergency and intensive care medicine and has life-saving potential in critical conditions. However, excessive oxygenation also has deleterious properties in various pathophysiological processes and consequently both clinical and translational studies investigating hyperoxia during critical illness have gained increasing interest. Reactive oxygen species (ROS) are notorious by-products of hyperoxia and play a pivotal role in cell signaling pathways. The effects are diverse but when the homeostatic balance is disturbed, ROS typically conserve a vicious cycle of tissue injury, characterized by cell damage, cell death and inflammation. The most prominent symptoms in the abundantly exposed lungs include tracheobronchitis, pulmonary edema, and respiratory failure. In addition, absorption atelectasis results as a physiological phenomenon with increasing levels of inspiratory oxygen. Hyperoxia-induced vasoconstriction can be beneficial during vasodilatory shock but hemodynamic changes may also impose risk when organ perfusion is impaired. In this context, oxygen may be recognized as a multifaceted agent, a modifiable risk factor and a feasible target for intervention. Although most clinical outcomes are still under extensive investigation, careful titration of oxygen supply is warranted in order to secure adequate tissue oxygenation while preventing hyperoxic harm.

INTRODUCTION

Oxygen is a vital element in human survival and plays a major role in a diverse range of biological and physiological processes. In medical practice, it is among the most universally used agents for the treatment of critically ill patients (1) and part of the routine treatment in acute shock and emergency medicine (2). In order to ensure sufficient oxygenation, oxygen therapy during mechanical ventilation, anesthesia and resuscitation usually exceeds physiological levels. However, Renaissance physician Paracelsus noted: "nothing is without poison – the poison is in the dose". This accounts for many aspects in medicine, but it may also be well applicable to the oxygen molecule (3). The concept of oxygen toxicity has been described in the late 19th century following the pioneering efforts of Lorrain Smith and Paul Bert, but it was not until a century later that the effects of hyperoxia were increasingly studied. Although several lines of evidence indicate that hyperoxia may be harmful, robust interventional studies are still limited. In order to develop adequate recommendations for optimal oxygen levels it is important to extend our current understandings of hyperoxia-induced injury. The aim of this review is to provide a comprehensive overview of the effects of hyperoxia from the bench and the bedside. The first part will focus on established insights and recent experimental and translational advances; the latter part addresses pathophysiological concepts, clinical studies and implications for therapy.

Pathogenesis from the benchside

Reactive oxygen species

Reactive oxygen species (ROS) are versatile molecules that can be essential in the regulation of intracellular signaling pathways and in host defense (4). However, ROS have also repeatedly been postulated to be of major significance in tissue damage, organ dysfunction and clinical disease. When referring to oxygen toxicity, it is frequently assumed that it is not oxygen itself that exerts toxic effects but merely the ROS that are generated as an undesirable byproduct of adenosine triphosphate synthesis during aerobic cellular metabolism. The implications for the lungs are probably the most prominent as lung tissue is continuously and abundantly exposed to oxygen and its byproducts. In physiological circumstances, ROS are formed in the electron transport chain during proton transport across the inner mitochondrial membrane. Mitochondrial oxidative phosphorylation is the most important source of oxygen species, but ROS may also be generated in response to exogenous stimuli, such as microbes, cytokines and xenobiotics (5). Antioxidant tasks are accomplished by enzymes as catalases, glutathione peroxidases, thioredoxins and peroxyredoxins. These enzymes use electron donors in order to avoid the intermediate formation of the hydroxyl radical (OH·), which is a strongly reactive oxidant. In this process superoxide dismutase (SOD) is an important antioxidant enzyme as it efficiently reduces the concentration of the superoxide anion ($O_2^{\cdot -}$), by facilitating its rapid conversion in hydrogen peroxide (H_2O_2) or oxygen (O_2). In general, ROS generation from mitochondria increases with oxygen tension and is dependent on the clinical balance between the underlying condition and oxygen supply (6). In response to bacterial invasion neutrophils can also produce large amounts of ROS that may initially be beneficial in the host defense against several pathogens. Fortunately, the lungs are

principally well protected against oxygen toxicity by adequate intra- and extracellular antioxidant activity. Beside this physiological activity, additional antioxidants can be recruited in the epithelial lining fluid (7). However, when the production of ROS exceeds the limits of counteraction by antioxidant responses, ROS concentrations reach inadequate levels and a cellular state of oxidative stress manifests. Oxidative stress refers to the imbalance caused by increased ROS formation or deficient oxidant suppressors (8). When antioxidant systems are insufficient during critical illness and mechanical ventilation, supplemental oxygen can cause accumulation of oxygen radicals and may initiate or perpetuate oxygen toxicity. Moreover, ROS control can be markedly influenced by ageing, genetic factors and pharmacochemical agents (6).

Cell death

When the delicate homeostatic balance is disturbed, oxidative stress leads to damage of nucleic acids, proteins and lipids, resulting in cell death by both apoptotic and necrotic pathways (9). Necrosis is characterized by incomplete apoptosis and supported by integrity loss of the cell membrane and cytoplasmic swelling. Programmed cell death by apoptosis can be achieved through extrinsic or intrinsic pathways, concomitantly. The *extrinsic* pathway is triggered by extracellular signals that stimulate intracellular apoptotic cascades after binding the cell membrane. The *intrinsic* apoptotic pathway is initiated by increased mitochondrial ROS formation. Subsequently, the opening of transition pores is facilitated making the outer mitochondrial membrane more permeable for pro-apoptotic components. These components can then pass to the cytoplasm and induce a state of intracellular stress. When this occurs in both endothelial and epithelial cells, lytic damage and cell death contribute to interstitial pulmonary edema and impaired gas exchange by means of alveolar collapse and disintegration of the alveolar-capillary barrier.

Cell damage and inflammatory pathways

In addition to direct cell death by necrosis or apoptosis, cellular disruption caused by hyperoxia and ROS has been shown to release endogenous damage-associated molecular pattern molecules (DAMPs) that alert the innate immune system (10-12). DAMPs, or alarmins, are cell fragments released during cellular dysfunction and sterile injury and act as pleiotropic modulators of inflammation. During oxidative stress, mitochondrial damage is a pivotal cause of extracellular hazardous content including both free radicals and DAMPs. As they resemble bacterial DNA, circulating mitochondrial DAMPs are efficiently recognized by pattern recognition receptors and activate polymorphonuclear neutrophils (PMNs). Subsequently, PMNs release interleukins and contribute to a sterile inflammatory reaction and, ultimately, neutrophil-mediated organ injury. In response to hyperoxia-mediated ROS production, resident lung cells initiate the release of various cytokines. Chemotactic factors orchestrate the inflammatory response by attracting inflammatory cells to the pulmonary compartment. Recruited neutrophils and monocytes are in turn significant sources of additional ROS, conserving a vicious cycle leading to further tissue damage (Fig. 1).

Under enduring conditions of injury to pulmonary epithelium and increasing alveolar permeability, cytokines can translocate from the alveolar space to the systemic circulation, creating

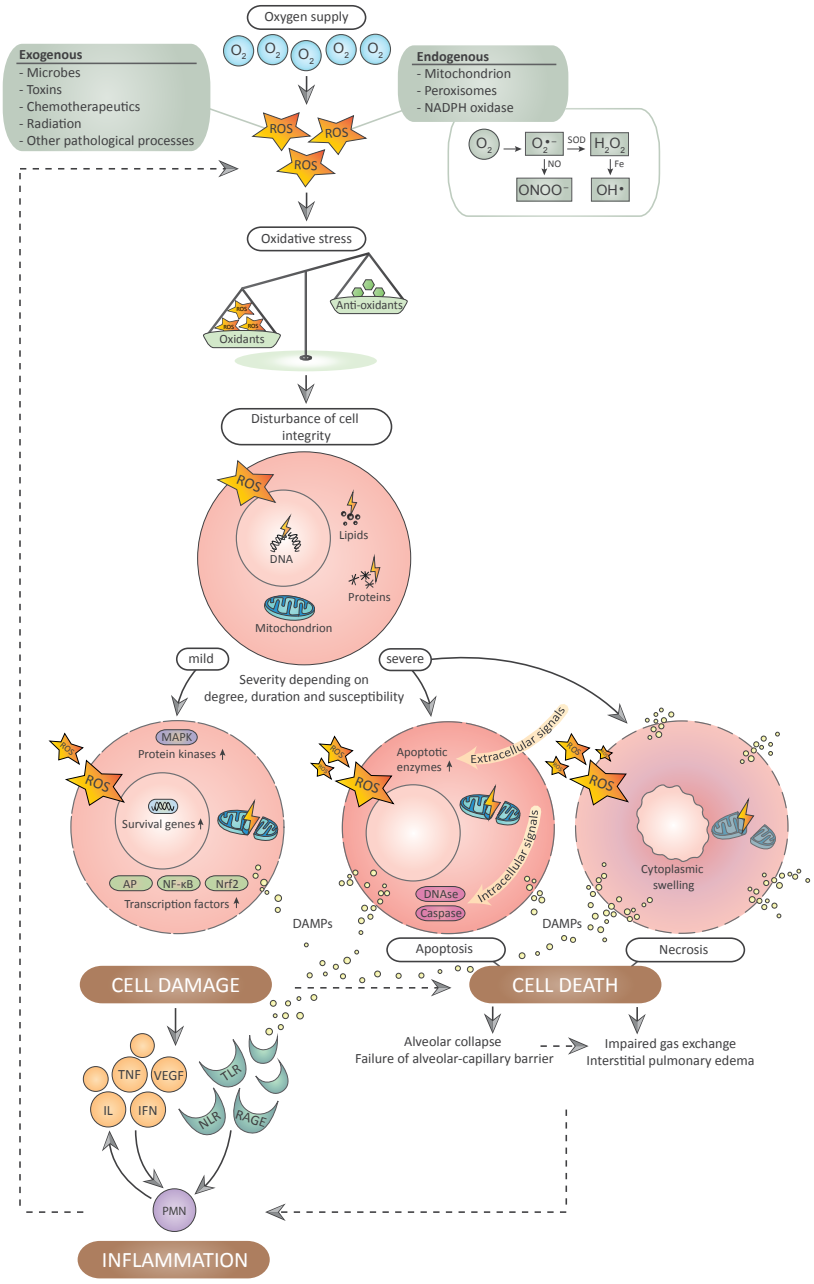

Figure 1. Vicious cycle of hyperoxia induced cell injury.
AP, activator protein; DAMP, damage-associated molecular pattern molecules; H_2O_2, hydrogen peroxide; IFN, interferon gamma; IL, interleukin; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NLR, nodlike receptor; Nrf2, nuclear factor-2 erythroid related factor-2; O_2, oxygen; O_2 ·−, superoxide; OH·, hydroxyl radical; ONOO−, peroxynitrite; PMN, polymorphonuclear neutrophil; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

a systemic inflammatory response, in which cytokines are efficiently activated and phagocytosis by alveolar macrophages is hampered (13). Cytokine concentrations decrease after long-term exposure, suggesting that a fast upregulation of inflammatory action is followed by a gradual impairment of the innate immune system (14). Besides mitochondrial damage, the inflammatory actions of oxygen are importantly modulated by the hypoxia-inducible transcription factor (HIF) (15, 16). HIF-1αis thought to be upregulated during relative changes in oxygenation and accordingly responds to normoxia as a relative hypoxic state directly after hyperoxia. Through this mechanism, intermittent hyperoxia may trigger a paradoxical phenomenon in which the genetic expression of inflammatory mediators and erythropoietin (EPO) is stimulated in the absence of true tissue hypoxia (17).

Animal studies

Principal insights in hyperoxia-induced mechanisms have been obtained from experimental models. The first animal studies documented structural morphologic and biochemical changes in the lungs of a wide variety of animal species that were exposed to hyperoxia (18). Pioneering studies using conscious dogs postulated that normobaric hyperoxia decreased metabolic rate and altered hemodynamics (19, 20). These findings were subsequently reproduced in primates in whom progressive pulmonary injury, interstitial edema and inflammatory activation were observed (21). In later experiments, biochemical effects of ROS and interventional targets on the molecular level were more intensively studied in spontaneously breathing animals in hyperoxic environments and showed both detrimental and protective potential (22-26). Recent experiments were performed in mechanically ventilated rodents, rabbits and pigs mimicking the clinical environment of critically ill patients (27-31). In this context, the interaction between injurious ventilation and concurrent hyperoxia was shown to transcend lung injury by alveolar distention alone (22, 32-35). However, studies in mechanically ventilated animals are usually restricted to short exposure periods (32, 34-38), even though hyperoxia may induce time-dependent inflammation (23). In order to improve our understanding of the impact of long-term exposure to both mechanical ventilation and hyperoxia, future studies involving mechanical ventilation of longer duration and with clinically relevant settings are essential for a robust representation of the ICU environment.

Pathogenesis from the bedside

Hyperoxia induced tissue injury

Under normobaric circumstances, the side-effects of oxygen are initially restricted to the lungs. However, when hyperoxia manifests for prolonged periods or under hyperbaric conditions, other organs are concurrently at risk as more oxygen is dissolved in plasma (6). The amount of dissolved oxygen will readily increase at partial pressures of arterial oxygen (PaO_2) exceeding 100 mmHg. Oxyhemoglobin saturation is nearly complete when PaO_2 approaches this level and the carrying capacity of hemoglobin is therefore quickly overcharged with increasing fractions of inspired oxygen (FiO_2).

The harmful effects depend on underlying conditions, duration and degree of the hyperoxic exposure. Rigid thresholds where harm exceeds the perceived benefits are not exactly known and

may vary between subgroups (39). Most pathophysiological changes originate rapidly and are rather universal effects, but the effects of hyperoxia are assumed to be time- and dose-dependent (40). In general, excessive oxygen supply causes absorption atelectasis by displacement of alveolar nitrogen. The progressive washout of nitrogen coincides with the abundant presence of oxygen in the alveoli which, driven by a steep pressure gradient, rapidly diffuses into the mixed venous blood. As a result, the alveolar volume is markedly reduced and leads to increased ventilation/perfusion mismatch by (partial) alveolar collapse and impaired gas exchange, which can be attenuated by applying positive end-expiratory pressure (PEEP) (41). Impaired mucociliary clearance by hyperoxia further contributes to obstructive atelectasis and altered surfactant metabolism facilitates adhesive atelectasis through alveolar instability and collapse. Several lines of evidence indicate further effects of breathing high oxygen levels in animals and healthy subjects (1, 42), but evidence of pulmonary toxicity in a clinical scenario is limited (43). The pathological features of this condition are commonly referred to as the Lorrain Smith effect (44) and are characterized by tracheobronchitis, which can be accompanied by pleuritic pain, bronchial irritation, cough and sore throat. Symptoms may spread from the upper airways into the lungs where diffuse alveolar damage manifests and contributes to edema, vascular leakage, arteriolar thickening, pulmonary fibrosis and emphysema, reflected by progressive paradoxical hypoxia, dyspnea and tachypnea. Additionally, prolonged hyperoxic exposure alters the microbial flora in the upper airways and further increases the risk of secondary infections and lethality. Notably, these pulmonary effects are often in addition to the primary (e.g. pneumonia) and secondary lung injury (e.g. ventilator-induced lung injury), which are accompanied by inflammatory responses.

The central nervous system is typically the first to reveal symptoms from excessive ROS formation. The spectrum of neurological symptoms is referred to as the Paul Bert effect and ranges from nausea, dizziness and headache to vision disturbances (retinal damage), neuropathies, paralysis and convulsions (1).

Vascular effects of hyperoxia have been well documented and may have both harmful and beneficial effects. Arterial hyperoxia increases the systemic vascular resistance and induces vasoconstriction, which may impair organ perfusion, especially in the cerebral and coronary region (45-47). Accompanying cardiovascular alterations result from even short term exposure and include a decrease in heart rate, stroke volume and cardiac output (48). However, hyperoxia is not a universal vasoconstrictor in all vascular regions and blood flow may be redistributed to the hepatosplanchnic circulation in septic shock (1, 49). Alternatively, the administration of oxygen promotes hemodynamic stabilization during vasodilatory shock, decreases intracranial pressure by cerebral vasoconstriction and preserves tissue oxygenation during hemodilution (2, 50).

Clinical studies

Critical care

Recent studies assessing the clinical effects of arterial hyperoxia or normobaric supplemental oxygen in critical care are listed in Table 1.

Table 1. Studies assessing the clinical effects of arterial hyperoxia or supplemental oxygen in subgroups of critically ill patients

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Eastwood 2012 (51)	ANZ	Cohort	2000-2009	MV	152680	-	Hypoxia in first 24h of admission was associated with increased in-hospital mortality, but hyperoxia was not.
de Jonge 2008 (52)	NET	Cohort	1999-2006	MV	36307	+	High FiO_2, and both low PaO_2 and high PaO_2 in first 24h of admission were associated with in-hospital mortality
Suzuki 2014 (53)	AUS	Before-after pilot	2012	MV	105	+/-	Conservative oxygen therapy in mechanically ventilated ICU patients was feasible and free of adverse biochemical, physiological, or clinical outcomes while allowing a marked decrease in excess oxygen exposure
Aboab 2006 (41)	FRA	Experimental	NA	ARDS	14	+/-	In mechanically ventilated patients with ARDS the breathing of pure oxygen leads to alveolar derecruitment, which is prevented by high PEEP.
Austin 2010 (54)	AUS	RCT	2006-2007	COPD	405	+	Titrated oxygen treatment significantly reduced mortality, hypercapnia, and respiratory acidosis compared with high flow oxygen in acute exacerbations of COPD
Cameron 2012 (55)	NZL	Cohort	2005-2008	COPD	180	+	Serious adverse clinical outcomes are associated with both hypoxaemia and hyperoxaemia during acute exacerbations
Perrin 2011 (56)	NZL	RCT	2007-2009	Asthma	106	+	High concentration oxygen therapy causes a clinically significant increase in transcutaneous CO_2 during severe exacerbations
Bellomo 2011 (57)	ANZ	Cohort	2000-2009	CA	12108	-	Hyperoxia did not have a robust or consistently reproducible association with mortality
Elmer 2014 (58)	USA	Cohort	2008-2010	CA	184	+	Severe hyperoxia was independently associated with decreased survival to hospital discharge
Ihle 2013 (59)	AUS	Cohort	2007-2011	CA	584	-	Hyperoxia within the first 24h was not associated with increased hospital mortality
Janz 2012 (60)	USA	Cohort	2007-2012	CA	170	+	Higher levels of the maximum measured PaO_2 were associated with increased in-hospital mortality and poor neurological status on hospital discharge
Kilgannon 2010 (61)	USA	Cohort	2001-2005	CA	6326	+	Arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Kilgannon 2011 (62)	USA	Cohort substudy	2001-2005	CA	4459	+	Supranormal oxygen tension was dose-dependently associated with the risk of in-hospital death
Kuisma 2006 (63)	FIN	RCT pilot	NA	CA	28	-	No indication that 30% oxygen with SpO_2 monitoring did worse than the group receiving 100% oxygen.
Lee 2014 (64)	KOR	Cohort	2008-2012	CA	213	-	Mean PaO_2 was not independently associated with in-hospital mortality
Nelskylä 2013 (65)	AUS	Cohort	2008-2010	CA	122	-	No statistically significant differences in numbers of patients discharged from the hospital and thirty day survival between patients with hyperoxia exposure and no exposure
Spindelboeck 2013 (66)	AUT	Cohort	2003-2010	CA	145	-	Increasing PaO_2 was associated with a significantly increased rate of hospital admission and not with harmful effects
Vaahersalo 2014 (67)	FIN	Cohort	2010-2011	CA	409	-	Hypercapnia was associated with good 12-month outcome, but harm from hyperoxia exposure was not verified
Miñana 2011 (68)	ESP	Cohort	2003-2009	ADHF	588	-	Admission PaO_2 was not associated with all-cause long-term mortality
Ranchord 2012 (69)	NZL	RCT pilot	2007-2009	STEMI	136	-	No evidence of benefit or harm from high-concentration compared with titrated oxygen
Stub 2012 (70)	AUS	RCT	2011-2014	STEMI	441	+	Supplemental oxygen therapy in patients with STEMI but without hypoxia increased myocardial injury, recurrent myocardial infarction, cardiac arrhythmia, and was associated with larger myocardial infarct size at six months. Further results anticipated.
Sutton 2014 (71)	ANZ	Cohort	2003-2012	Post cardiac surgery	83060	-	No association between mortality and hyperoxia in the first 24 h in ICU after cardiac surgery
Ukholkina 2005 (72)	RUS	RCT	NA	AMI	137	-	Inhalation of 30-40% oxygen within 30 min prior to endovascular myocardial reperfusion and within 4h thereafter reduced the area of necrosis and peri-infarction area, improved central hemodynamics, and decreased the rate of postoperative rhythm disorders as compared with patients breathing ambient air

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Zughaft 2013 (73)	SWE	RCT	NA	ACS	300	-	The use of oxygen during PCI did not demonstrate any analgesic effect and no difference in myocardial injury measured with troponin- t or in the morphine dose
Asher 2013 (74)	USA	Cohort	NA	TBI	193	-	PaO_2 threshold between 250 and 486 mmHg during the first 72 h after injury was associated with improved all-cause survival, independent of hypocarbia or hypercarbia
Brenner 2012 (75)	USA	Cohort	2002-2007	TBI	1547	+	Hyperoxia within the first 24h of hospitalization was associated with worse short-term functional outcomes and higher mortality
Davis 2009 (76)	USA	Cohort	1987-2003	TBI	3420	+	Both hypoxemia and extreme hyperoxemia were associated with increased mortality and a decrease in good outcomes
Quintard 2014 (77)	SUI	Cohort	2009-2013	TBI	36	+	Incremental normobaric FiO_2 levels were associated with increased cerebral excitotoxicity, independent from brain tissue oxygen and other important cerebral and systemic determinants
Raj 2013 (78)	FIN	Cohort	2003-2012	TBI	1116	-	Hyperoxemia in the first 24h of admission was not predictive of 6-month mortality
Rincon 2013 (79)	USA	Cohort	2003-2008	TBI	1212	+	Arterial hyperoxia was independently associated with higher in-hospital case fatality
Jeon 2014 (80)	USA	Cohort	1996-2011	Stroke	252	+	Exposure to hyperoxia was associated with delayed cerebral ischemia
Rincon 2014 (81)	USA	Cohort	2003-2008	Stroke	2894	+	Arterial hyperoxia was independently associated with in-hospital death as compared with either normoxia or hypoxia
Roffe 2011 & Ali 2013 (82, 83)	UK	RCT pilot	2004-2008	Stroke	289	-	Routine oxygen supplementation started within 24 h of hospital admission with acute stroke led to a small improvement in neurological recovery at 1 week, but no outcome differences were observed at 6 months
Rønning 1999 (84)	NOR	Quasi-RCT	1994-1995	Stroke	310	+	Supplemental oxygen should not routinely be given to nonhypoxic patients with minor or moderate strokes
Singhal 2005 (85)	USA	RCT pilot	NA	Stroke	16	-	High-flow oxygen therapy is associated with a transient improvement of clinical deficits and MRI abnormalities

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Young 2012 (86)	ANZ	Cohort	2000-2009	Stroke	2643	-	Worst arterial oxygen tension in the first 24h was not associated with outcome
Stolmeijer 2014 (87)	NET	Cohort	NA	Sepsis	83	-	No association between mortality and hyperoxia, nor between lower FiO_2 and other detrimental effects

+, study found harm from supplemental oxygen or arterial hyperoxia; -, no harm found from supplemental oxygen or arterial hyperoxia.
ACS, Acute coronary syndrome; ADHF, Acute decompensated heart failure; AMI, Acute myocardial infarction; ARDS, Acute respiratory distress syndrome; CA, Cardiac arrest; CO2, Carbon dioxide; COPD, Chronic obstructive pulmonary disease; FiO2, Fraction of inspired oxygen; ICU, Intensive care unit; MRI, Magnetic resonance imaging; NA, Not available; PaO2, Partial pressure of arterial oxygen; PCI, Percutaneous coronary intervention; MV, Mechanical ventilation; PEEP, Positive end-expiratory pressure; RCT, Randomized Controlled Trial; SpO2, Oxyhemoglobin saturation; STEMI, ST-segment elevation myocardial infarction; TBI, Traumatic brain injury

As highlighted in recent meta-analyses (88, 89), the effects on major clinical end points are conflicting and may be partially explained by heterogeneous methodology and subgroup differences in critically ill patients. Pooled effect estimates favoring normoxia are quite consistent but the harmful effects were previously shown to be impacted by the definition of hyperoxia and may be more pertinent to specific subgroups and at specific moments of admission.

It is well-established that the use of higher FiO_2 can lead to progressive hypercapnia during a state of chronic compensated respiratory acidosis and serious adverse outcomes have been shown in acute exacerbations of chronic obstructive pulmonary disease (COPD) or asthma (54-56). Likewise, high fractions of oxygen in the inspired air and arterial blood have been associated with increased mortality in mechanically ventilated patients (52).

Owing to a striking lack of robust clinical trials, a causal relationship is still uncertain and both the magnitude and direction of the associations depend on the adjustment for illness severity scores, FiO_2 and other confounders (51, 52). Future randomized controlled studies are urgently needed to definitively elucidate the causal effects of oxygenation targets and derangements on clinical outcomes of critically ill patients.

Excessive oxygenation may be most intensively studied after resuscitation from cardiac arrest as both the vascular alterations and the ischemia and reperfusion injury are hypothesized to be hazardous (90). In a dose-dependent manner, hyperoxia has been linked to worse outcome in these patients. (58, 60-62). The adverse association was not systematically reproduced, possibly due to heterogeneity in study methods (57, 59, 64, 66, 67, 91). The only randomized controlled trial in the postresuscitation period found that 30% oxygen ventilation was not worse in comparison with 100% oxygen, but the study was underpowered to detect significant differences (63). In view of all recent data, supplemental oxygen administration during resuscitation still appears desirable, while hyperoxia should be avoided in the post-resuscitation phase and saturation should be targeted at 94–96% (90, 92).

A large number of both experimental and clinical studies have primed pediatricians with great awareness of the risks of hyperoxia. For neonatal resuscitation, the routine use of 100% oxygen has been abandoned after numerous associations with myocardial, neurologic and kidney injury, retinopathy, inflammation and increased mortality (93, 94). However, strict adherence to lower target ranges of oxygen saturation among preterm infants did not significantly reduce disability or deaths (95). Results from a prospective large-scale meta-analysis investigating the most appropriate level of oxygenation for extremely preterm neonates suggested that functional oxyhemoglobin saturation (SpO_2) should be targeted at 90-95% in the postnatal period (96).

Hyperoxia-induced vasoconstriction poses a major concern in the management of acute coronary syndromes and guidelines increasingly suggest a restriction of supplementary oxygen to only those at increased risk for hypoxia (97). Indeed, oxygen therapy has not been shown to be beneficial after acute myocardial infarction and may even be harmful causing a marked reduction in coronary blood flow and myocardial oxygen consumption (98, 99). The vasoconstriction caused by hyperoxia may be of special concern in the acute setting before reperfusion. The AVOID trial aimed to definitively qualify the role of supplemental oxygen in acute myocardial infarction (70) and found increased myocardial injury, recurrent myocardial infarction, cardiac arrhythmia and

infarct size at six months (100). In contrast, a smaller trial observed a beneficial effect of 30-40% oxygen inhalation over controls both during occlusion and reperfusion (72). Hemodynamic effects may also be pertinent to patients with acute ischemic stroke, who do not appear to benefit from increased survival after prolonged treatment with oxygen (82, 84).

Despite the theoretical benefit of decreasing intracranial pressure through cerebral vasoconstriction, hyperoxia has repeatedly been associated with delayed cerebral ischemia and increased cerebral excitotoxicity after cerebrovascular incidents (77, 80, 81). Interestingly, the synergistic combination of hyperbaric and normobaric hyperoxia was recently found to have potential therapeutic efficacy in severe traumatic brain injury (101). However, observational data in patients with traumatic brain injury, ischemic stroke, subarachnoid or intracerebral hemorrhage, remain equivocal (74-76, 78, 79, 86).

Perioperative care

Liberal oxygen supply is usually accepted in perioperative care, in order to avoid potentially life-threatening consequences of hypoxia during surgery. Further effects of perioperative hyperoxia have been comprehensively summarized in meta-analyses, enrolling over 7,000 patients, and generally showed a reduced risk of surgical site infections and postoperative nausea, without luxation of postoperative atelectasis (102, 103). However, risks may outweigh benefits in specific age groups (39) and different subsets. This was recently highlighted in patients undergoing cancer surgery where 80% oxygen supply in the perioperative setting showed a significantly increased long-term all-cause mortality compared with those randomized to 30% (104).

Implications for therapy

Several therapeutic options that limit the harmful effects of hyperoxia can be contemplated, but prevention of excessive oxygenation is likely to be the most effective strategy. A rational approach may be a more conservative administration strategy in which oxygen is titrated to a lower tolerable level in order to prevent iatrogenic harm while preserving adequate tissue oxygenation. Recently, a pilot interventional study showed that conservative oxygen therapy in mechanically ventilated patients in the intensive care unit (ICU) can be feasible and free of adverse outcomes, while decreasing excess oxygen exposure (53). Importantly, when the risks for severe tissue hypoxia are pronounced, ample oxygen supply remains vital and should be started immediately to increase oxygen delivery and preserve tissue oxygenation. Also, oxygen may aid hemodynamic stabilization, decrease intracranial pressure and can be used to stimulate erythropoietin and increase hemoglobin, when using intermittent hyperoxia as a paradoxical trigger for HIF expression.

Experimental interventions to decrease harm from hyperoxia are targeted at numerous steps in the pathway of ROS-induced damage. The primary source for intervention in the oxidative cycle is inhibition of oxidant generation, either quantitatively or qualitatively. Bleomycin and amiodarone are well-known originators of drug-induced pulmonary disease and should be avoided to minimize preventable ROS formation (105, 106). Limiting the exposure to other exogenous stimuli or preventing electron leakage in the electron transport chain may protect the mitochondria,

but this strategy proves cumbersome in actual practice. Although the clinical applicability has been questioned due to little or no preventative or therapeutic effect, the supply of antioxidant enzymes may be a potentially feasible approach to facilitate the conversion, avoid the intermediate formation, and reduce the concentration of strongly reactive oxidants. However, some of these antioxidants may actually have pro-oxidant properties depending on their concentration and interaction with other molecules. The neutralizing effect of antioxidants may also not be sufficient to secure metabolic stability, even when secondary inflammation is mitigated. Finally, oxidant scavenging can shift the balance towards harm when the role of oxidants in cell signaling pathways is suppressed (107).

As an alternative, pathways of cell integrity, cell death, and inflammation may be targeted to reduce further damage and enhance the defense against oxygen radicals. Experimental research suggests protective effects through modulation of protein kinases (108, 109) and transcription factors (110-113). Moreover, numerous preclinical studies have demonstrated that manipulation of chemokines, cytokines (13, 114), growth factors (115), receptors (116-118) and DAMPs (11, 12, 119) may limit hyperoxia induced injury, but these targets all remain to be evaluated at the bedside.

CONCLUSION

Although oxygen remains of life-saving importance in critical care, accumulating evidence has demonstrated the prominent role of hyperoxia and the consequent formation of reactive oxygen species in the pathogenesis of several life-threatening diseases. The toxic effects of supraphysiological oxygen concentrations are driven by cell damage, cell death and inflammation. These aspects are of special concern in the pulmonary compartment, where absorption atelectasis impairs respiratory function at high inspiratory oxygen levels. The cerebral and coronary circulations are at specific risk when vascular alterations manifest. Long-term exposure to hyperoxia impairs the innate immune response and increases susceptibility to infectious complications and tissue injury. Given that critically ill patients are prone for inflammation, cardiovascular instability and depleted antioxidant mechanisms, the most rational practice may be to supply oxygen conservatively and titrate the therapy carefully to the patient's needs. However, our understanding of oxygen toxicity is limited in humans and conflicting findings hamper the constitution of compelling guidelines. Further research is warranted to study hyperoxia induced effects in clinical practice, to elucidate time- and dose-response relationships, and to provide evidence-based oxygenation targets and interventions through robust clinical trials.

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LIST OF ABBREVIATIONS

DAMP, damage-associated molecular pattern molecule; FiO_2, fraction of inspired oxygen; HIF, hypoxia-inducible factor; ICU, intensive care unit; PaO_2, partial pressure of arterial oxygen; PMN, polymorphonuclear neutrophil; ROS, reactive oxygen species

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