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Advances in the Application of Oxygen Therapy in the Perioperative Period

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Abstract: *Oxygen is the third most abundant element in the universe after hydrogen and helium, and it is the fundamental substance upon which life on Earth depends. Oxygen plays a crucial role in the production of adenosine triphosphate (ATP) within mitochondria. Glucose is converted into pyruvate through glycolysis, which is then transformed into acetyl-CoA. This latter compound subsequently enters the mitochondrial tricarboxylic acid (TCA) cycle, where oxidative phosphorylation generates ATP. During this oxidative phosphorylation process, oxygen serves as the final electron acceptor. This physiological process is essential for the survival of most cells in the body, with the brain and heart being particularly susceptible to hypoxia. Therefore, maintaining stable oxygenation in patients entering the operating room is a key management goal for anesthesiologists. This article reviews the effects of perioperative oxygen therapy on vital organs, surgical site infections, and long-term outcomes. It aims to discuss the important clinical value of oxygen during the perioperative period and provide guidance for further clinical research and application.*

Keywords: *Oxygen; Recovery Period; Inhaled Oxygen Concentration*

1. The physiological mechanism by which the body perceives oxygen

Mammals have evolved a complex physiological network that involves the capture, binding, transportation, and transmission of molecular oxygen. Hypoxia or hyperoxia triggers a series of signaling pathways that activate transcriptional, metabolic, and morphological responses to maintain cellular homeostasis.

At the physiological level, when arterial PO_2 decreases, hypoxic signals are transmitted from glomus type I cells in the carotid and aortic bodies to the respiratory center, reflexively enhancing respiratory drive [1-3]. Hypoxic pulmonary vasoconstriction is a critical oxygen homeostasis mechanism in the pulmonary vasculature, triggered by mitochondrial redox and reactive oxygen species (ROS). This signaling involves coordinated responses between the electron transport chain (ETC) and redox-sensitive potassium and calcium channels, causing pulmonary artery constriction in response to low alveolar PO_2. Consequently, blood is redirected to better-oxygenated lung segments, optimizing the ventilation/perfusion ratio and oxygen delivery [4-6]. At the cellular level, erythropoietin-producing cells within the renal stroma sense discrepancies between oxygen supply and demand, regulating erythropoiesis by modulating erythropoietin (EPO) secretion levels [7,8]. At the molecular level, hypoxia-inducible factor (HIF) is a transcription factor crucial for hypoxia-induced gene regulation. Hypoxia activates oxygen-dependent post-translational modifications and nuclear translocation, increasing HIF-1 protein expression and stability. HIF-1 synergistically regulates tissue oxygen supply and energy metabolism by inducing the transcriptional expression of downstream target genes [9]. Early studies demonstrated that HIF-1 promotes erythropoiesis via EPO, induces vascular endothelial growth factor to enhance angiogenesis, and increases glycolysis [10,11].

Furthermore, mitochondria and ROS play extensive roles in eukaryotic functional responses to PO_2 changes [12]. ROS are inevitable byproducts of cellular aerobic metabolism, primarily formed by the combination of electrons and oxygen at electron transport chain (ETC) complexes I and III to generate superoxide anion radicals (O_2^-) [13,14]. Approximately 1–2% of O_2 consumed by mitochondria is utilized for ROS formation. At low to moderate concentrations, ROS participate in cellular activities such as pathogen defense, signaling, and mitosis. Their production rate increases with rising oxygen levels [15,16]. However, when oxidants and antioxidants become imbalanced, ROS induce oxidative stress, causing

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damage to cellular nucleic acids, lipids, and proteins, which impairs cellular function and reduces viability [17-19]. Concurrently, ROS generated by mitochondria enhances HIF1-α stability under hypoxic conditions [20], thereby participating in various fundamental and adaptive physiological responses that maintain organismal homeostasis [21]. For decades, numerous studies have focused on the potential of non-targeted antioxidant therapies to restore normal physiological functions under oxidative stress conditions. Common antioxidants such as vitamin C, vitamin E, and ubiquinone 10 have been demonstrated in cellular or animal model experiments to inhibit oxidative bursts, while also affecting healthy tissues unaffected by oxidative damage. Overall, the clinical value of non-targeted antioxidant therapy remains controversial.

2. Effects of Perioperative Oxygen Therapy on Vital Organ Function

2.1 Lungs

Short-term perioperative hyperoxia reduces pulmonary vascular resistance, increasing pulmonary blood volume and redistributing regional pulmonary perfusion to improve hypoxemia caused by ventilation-perfusion mismatch. However, exposure to pure oxygen in healthy individuals may cause atelectasis, impaired mucociliary clearance, tracheobronchitis, alveolar protein leakage, enhanced leukotriene expression in alveolar macrophages, and increased alveolar neutrophils. Substantial evidence indicates that inhaling high-concentration oxygen is detrimental to lung function, including impaired gas exchange due to ROS-induced cytotoxicity and atelectasis caused by alveolar collapse [22]. Ventilator-associated lung injury and anesthetic drug toxicity are unavoidable during mechanical ventilation, factors that may also synergize with hypoxia-induced lung injury.

Consequently, postoperative pulmonary complications (PPC) are relatively common, occurring at a rate of approximately 2% to 19%. They significantly prolong hospital stays, increase mortality rates, and elevate healthcare costs. Staehr-Ryed et al. [23] retrospectively analyzed clinical data from 73,922 patients undergoing non-cardiac surgery and found no benefit from hyperoxic therapy. Logistic regression analysis demonstrated that the risk of PPC increased with rising inspired oxygen concentrations. The severity of atelectasis also increased in a dose-dependent manner with rising FiO_2, and the use of high-concentration oxygen ventilation during surgery.

2.2 Brain

As the world enters an era of aging populations, more elderly individuals will undergo surgical anesthesia, making perioperative protection of vital organs critically important. Although the adult brain weighs only approximately 1400 g, it accounts for nearly 20% of the body's basal oxygen consumption. Even transient ischemia can cause significant neurodegeneration. In healthy individuals, hyperoxia induces cerebral vasoconstriction, reducing cerebral blood flow by 11% to 33% and causing neurological injury. Consequently, relevant guidelines recommend maintaining oxygen saturation between 94% and 98% in critically ill patients with neurological complications.

Perioperative neurocognitive disorders (PND) represent manifestations of perioperative neurological injury and constitute a common postoperative complication, particularly among elderly patients undergoing major surgery or cardiac procedures. In 2009, Slater et al. [24] found that a regional cerebral oxygen saturation ($rScO_2$) desaturation fraction below 50% was significantly associated with cognitive decline and prolonged hospitalization after coronary artery bypass grafting (CABG). Another prospective study indicated that low $rScO_2$ at the end of cardiac surgery was associated with postoperative cognitive decline. These findings suggest that cerebral hypoxemia during surgical anesthesia may be a contributing factor to PND. Concurrently, factors such as unsaturated lipids, glucose, mitochondria, calcium, glutamate, antioxidant defense systems, and redox-active metal ions render the brain highly susceptible to oxidative stress [6]. A recent retrospective analysis by Kupiec et al. [25] indicated that hyperoxia during cardiopulmonary bypass may be a risk factor for postoperative delirium (POD). The POD-positive group exhibited a higher incidence of severe hyperoxia ($PaO_2 \geq 200$ mmHg) (100% vs. 78%), with the highest delirium incidence observed at PaO_2 approximately 250 mmHg. Lopez et al. [26] observed 310 cardiac surgery patients, finding that hyperoxic reperfusion following intraoperative cerebral hypoxia was independently associated with POD after cardiac surgery, suggesting oxidative damage may mediate this association. Furthermore, the degree of cerebral hyperoxia, rather than hypoxia, correlated with POD occurrence. While this study examined the association between cerebral oxygen saturation and POD, confounding factors inherent to cardiac surgery and potential inaccuracies in NIRS technology

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necessitate prospective validation of these findings. Building on this, Shahzad et al. [27] prospectively examined the relationship between intraoperative FiO_2 and PND. Their findings showed no clear association between FiO_2 levels and PND, postoperative stroke, or TCI. However, the brain exhibits high sensitivity to oxygen. Both hypoxemia during surgical anesthesia and hyperoxic reperfusion following hypoxia can adversely affect cerebral function. Maintaining stable cerebral metabolic oxygenation through appropriate monitoring during surgery is therefore critically important.

2.3 Cardiovascular System

Extensive evidence indicates that varying levels of oxygenation exert broad effects on the cardiovascular system. During the perioperative period, hyperoxia exerts distinct actions on systemic and pulmonary circulation, including increased afterload and reduced preload, ultimately diminishing cardiac output [28]. Vascular resistance exhibits a dose-dependent increase. Waring found that administering supplemental oxygen via a face mask for 1 hour to healthy volunteers reduced heart rate and cardiac index while increasing systemic vascular resistance and mean arterial pressure [29]. Coronary artery resistance significantly increased (21.5%–40.9%), and a significant decrease in coronary blood flow (mean reduction of 17.1% in healthy subjects and 7.9%–28.9% in coronary artery disease patients). Stub reported that supplemental oxygen therapy in non-hypoxic ST-segment elevation myocardial infarction (STEMI) patients may increase early myocardial injury and infarct size at 6 months post-onset [30]. Consequently, the 2017 European Society of Cardiology guidelines for STEMI management do not recommend routine oxygen therapy for patients with $SaO_2 \geq 90\%$ [31]. Furthermore, numerous studies have demonstrated the protective effects of hyperoxia pretreatment on ischemic myocardium: research indicates that hyperoxia pretreatment reduces myocardial infarction size after ischemia-reperfusion, decreases reperfusion-induced arrhythmias, and improves cardiac function [32-34].

Thus, hyperoxia preconditioning anticipated hypoxia may exert beneficial effects by preventing or mitigating hypoxic injury. Given hyperoxia's physiological impact on the cardiovascular system and its inherent oxidative stress and pro-inflammatory effects, oxygen therapy in patients with concomitant cardiovascular disease or low cardiopulmonary reserve requires careful balancing of oxygenation benefits against adverse consequences.

3. Other Effects

3.1 Surgical Site Infection

The World Health Organization defines surgical site infection (SSI) as an infection anatomically related to an operating room surgical procedure that was not present before surgery. This report recommends that adult patients undergoing general anesthesia with endotracheal intubation receive 80% FiO_2 during surgery. The antimicrobial effect of oxygen was first proposed by Knighton et al. in the 1980s. The oxidative killing of pathogens depends on O2- generated by reduced coenzyme II, with reaction rates dependent on PO2. In 2000, Greif et al. [35] published a study showing that infection risk was negatively correlated with postoperative tissue oxygenation. Patients undergoing colorectal resection with FiO_2 of 80% demonstrated a significantly reduced incidence of SSI. Belda et al. [36] enrolled 300 colorectal resection patients who were randomly assigned to FiO_2 of 30% or 80% during surgery and for 6 hours postoperatively. The results showed that 24.4% of patients receiving 30% oxygen developed SSI, compared to only 14.9% of those receiving 80% oxygen. Although many studies have suggested that inhaling high-concentration oxygen may benefit SSI outcomes, their sample sizes have been far too small to detect significant differences. Additionally, high risk of bias in these studies means that the benefits of perioperative hyperoxia require further investigation. Kurz et al. [37] conducted a prospective intervention study involving 5,749 patients undergoing intestinal surgery and found that supplemental oxygen did not reduce SSI rates. In summary, there is currently no strong evidence supporting the use of high-concentration oxygen inhalation to reduce SSI rates in patients undergoing all types of surgery. Large-scale, multicenter, prospective randomized controlled trials are still needed to confirm this.

3.2 Long-Term Prognosis

Eastwood et al. [38] conducted a retrospective analysis of medical records from 152,680 mechanically ventilated patients, suggesting a positive correlation between in-hospital mortality and hypoxia, independent of the patient's high PaO_2 level within 24 hours before ICU admission. Another multicenter prospective study showed no significant difference in ventilator use or mortality between conservative

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oxygen therapy and conventional oxygen therapy groups; however, conservative oxygen therapy may benefit patients with suspected hypoxic-ischemic encephalopathy [39]. Consistent with prior findings that free oxygen therapy increases mortality without improving other key outcomes [40], a 2015 meta-analysis by Helmerhorst et al. [41] involving over 49,000 patients demonstrated a hospital mortality odds ratio of 1.38 for hyperoxic patients, irrespective of admission diagnosis. Building on this, another study by Helmerhorst et al. [42] indicated that severe hyperoxia (PaO_2 > 200 mmHg) showed higher mortality than mild hyperoxia (PaO_2 120–200 mmHg), with adjusted in-hospital mortality being lowest within the PaO_2 range of 120–160 mmHg. This aligns with findings from a prior study involving over 36,000 patients, where de Jonge et al. [43] revealed a U-shaped relationship between mortality and PaO_2, with lower mortality rates observed within the 110–150 mmHg range. Both lower and higher PaO_2 levels were associated with increased mortality risk. These findings underscore the hazards of prolonged hyperoxia, where even mildly elevated oxygen levels combined with cumulative exposure time can lead to adverse patient outcomes. Therefore, the potential risks of perioperative oxygen therapy should not be assessed solely by pulse oximetry or PaO_2; more precise indicators need to be established to predict risks and guide clinical management.

Some studies support the safety of high perioperative FiO_2, showing no increase in major complications or mortality. Currently, there is no compelling reason to restrict high FiO_2 use in patients without systemic complications. However, limited evidence suggests adverse effects of hyperoxia in patients with severe systemic complications.

4. Conclusion and Outlook

Ensuring adequate oxygenation and organ perfusion throughout surgery and the entire perioperative period is critical. In certain scenarios, short-term high-concentration oxygen therapy enhances treatment safety, such as preventing hypoxemia during anesthesia induction and intubation to delay apnea. Exposure to supraphysiological oxygen is often detrimental, potentially increasing inflammation and oxidative stress, with severe adverse effects on pulmonary function, microvascular perfusion, coronary, and cerebral blood flow. However, quantifiable oxidative stress induced by perioperative hyperoxia does not translate into increased postoperative pulmonary, cardiovascular, cerebrovascular complications, or mortality. Given that inhaling oxygen concentrations above 60% may increase adverse event risks and lacks compelling evidence of perioperative benefit, routine high-concentration oxygen inhalation during anesthesia and surgery is not supported. Instead, the harms associated with high-concentration supplemental oxygen and invasive mechanical ventilation strategies may outweigh the benefits of attempting complete reversal of arterial hypoxemia. Precise control of arterial oxygenation levels to avoid the harms associated with over-oxygenation or hypoxemia in perioperative or critically ill ICU patients, coupled with close monitoring and comprehensive, accurate assessment, represents a critical research priority that should be pursued. Given the high risk of bias and design flaws in previous studies, there is a need for low-bias, large-sample, long-term follow-up randomized clinical trials centered on critically ill patients. Concurrently, additional clinical trials should be designed to explore the value of physiological oxygenation and permissive hypoxemia in the perioperative period, improved oxygenation monitoring indicators, individualized oxygenation targets, and criteria for initiating and discontinuing oxygen therapy.

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