Oxygen in cardiac surgery: does more mean better?

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Abstract

Background: Supplemental oxygen has been using in clinical practice for a long time, but there are still many questions regarding to its pitfalls and advantages. On the one hand, high fraction of inspired oxygen speeds up gas resorption behind closed airways and promotes atelectasis formation and pulmonary shunt. Hyperoxia may cause vasoconstriction, thereby compromising perfusion and hence, actual oxygen delivery. Hyperoxia may increase oxidative stress by boosting the production of reactive oxygen species, consequently aggravating ischemia-reperfusion injury. On the other hand, the vasoconstrictive stimulus of short-term exposure to hyperoxia before sustained ischemia may act as a preconditioner, with attenuation of ischemia-reperfusion injury. Hyperoxia induced vasoconstriction may counteract systemic inflammation induced vasoplegia and reduce vasopressor requirements. Hyperoxia may reduce gas microemboli by denitrogenation. Consequently, arterial oxygen tension is kept mainly at supraphysiologic level, especially during operations and cardio-pulmonary bypass.
Aim: The aim of the present review is to update information about optimal oxygen concentration and oxemia level. Oxygen is a crucial element in perioperative management of cardiac surgery patients. It's obligatory to determine whether the changes accompanied with supraphysiologic level of oxygen are benign or they translate into a worsening of clinical outcomes.
Methods: Major databases were systematically searched for clinical trials comparing oxygenation strategies for adult cardiac surgery.
Results: There is a trend towards lower PaO_2 targets in the most recent RCTs that may be indicative of a change in clinical practice towards more conservative oxygenation strategies. Although the optimal intraoperative oxygenation strategy remains uncertain, the results of recents clinical trials indicate that moderate hyperoxia does not worsen clinical outcome after cardiac surgery
Conclusions: Mild to moderate hyperoxia may be successfully used in cardiac surgery. The correct timing of applying supraphysiologic level of oxygen might be the key to reliably defeat patients from hypoxia and avoid hyperoxia induced undesirable consequences. **(TCM-GMJ June 2024; 9 (1):P62-P66)**

Keywords: oxygen, cardiac surgery, anesthesia, hyperoxia

Introduction

In cardiac surgery high concentrations of oxygen are routinely administered, with the intention of preventing cellular hypoxia. Oxygen delivery to the tissues is threatened during bypass due to increased microcirculatory heterogeneity. The augmented oxygen diffusion distance may impair oxygen delivery and organ function. Other factors that may reduce oxygen delivery to tissues include: hypothermia; fluid shift; myocardial dysfunction; blood loss; anemia; and transfusion.(1) With this in mind, it may be intuitively correct to maintain PaO_2 clearly above physiological values (mostly defined as 75-100 mmHg), to increase the oxygen gradient between capillaries and tissue and reduce the risk of cellular hypoxia. Compared with normoxic strategies, the impact of hyperoxia on postoperative organ dysfunction, length of stay and mortality in adult cardiac surgery patients appears to have been minimal, though the evidence base is highly heterogeneous with marked variability in study design and is also at risk of bias.(2) The level of oxygen that patients should be exposed to during cardiac surgery is an important clinical question that has been asked by investigators for over two decades. What makes this question so intriguing is the simplicity of the intervention, the complexity of its multisystem effects, and the potential to make a real difference to clinically important outcomes. The RCTs studying the impact of hyperoxia during adult

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Received March 08, 2024; accepted May 2 , 2024.
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cardiac surgery were heterogenous in design, particularly in two key areas: the timeline over which the oxygenation strategy being studied was employed and the degree of hyperoxia or normoxia participants were exposed to. Additionally, some trials subjected participants to a constant FiO_2 whereas others adjusted FiO_2 to meet a PaO_2 target. There is no universal consensus on what represents a truly hyperoxic PaO_2 during cardiac surgery.

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Methods

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Results and discussion

PaO_2 targets were so disparate across studies that the normoxic targets in some trials were higher than the hyperoxic targets in others. There are also major differences between trials as to the timing of when the impact of hyperoxia is examined, with some focusing on CPB only, whereas others have looked at oxygenation strategies starting from the time of anesthetic induction to throughout postoperative ICU care. The absence of a standard definition of hyperoxia in cardiac surgery makes it difficult to draw any solid conclusions from existing trials. There is no agreement in the literature as to what conditions should be considered normoxic or hyperoxic during cardiac surgery. The differences in outcomes between the groups were found in previous trials that used high targets of hyperoxia ($\geq$ 300 mmHg). There is a trend towards lower PaO_2 targets in the most recent RCTs that may be indicative of a change in clinical practice towards more conservative oxygenation strategies. This trend is based on evidence from the myocardial infarction and cardiac arrest literature suggesting that high oxygen levels during reperfusion after ischemia may have deleterious effects.(3),(4). When comparing moderate, near-physiologic level of hyperoxemia with normoxemia, there are no significant differences between the groups. The last two trials in the Table 1 are the RCTs of later period, that have attempted to demonstrate that avoidance of hyperoxia during cardiac surgery reduces ischemia-reperfusion injury and leads to improved clinical outcomes.(5),(6). McGuinness and colleagues randomized 298 elective cardiac surgery patients to either avoidance of intraoperative hyperoxia (with a PaO_2 target of 75-90 mmHg) or to usual care under hyperoxic (mean, 178 mmHg) conditions. They found no difference between groups for the primary outcome of postoperative acute kidney injury, or any of the secondary outcomes. Smit and colleagues randomized 50 elective coronary artery bypass graft surgery patients to either a PaO_2 target of 130 to 150 mmHg on CPB (and 80-100 mmHg in the immediate postoperative period) or a target of 200 to 220 mmHg on CPB (and 130-150 mmHg postoperatively). The conservative oxygen strategy did not offer any benefit with respect to the primary outcome of myocardial injury (defined by suitable CK-MB and Troponin-T thresholds).

Until there is definitive evidence to suggest otherwise, hyperoxia during cardiac surgery should be considered a standard of care.(7) The morbidity and mortality associated with cardiac surgery using cardiopulmonary bypass remains high despite advances in surgical technique and anesthetic management. Much of this morbidity can be attributed to tissue malperfusion and hypoxia in the perioperative period.(8) CPB-related microcirculatory heterogeneity, cardiac dysfunction, hypothermia, fluid shifts, and allogeneic blood transfusion all contribute to impaired tissue oxygenation. Dissolved oxygen may be of particular benefit in this setting, where patients often are hemodiluted and a high level of PaO_2 can increase delivery of this dissolved component. The increased PaO_2 is also thought to impart an increased oxygen reserve, providing a buffer in the event of significant interruption of ventilation or profound hemodynamic instability. Targeting supraphysiologic oxygenation during cardiac surgery is an effective strategy to guard against hypoxia, the deleterious effects of which are well established. Hyperoxia has multiple direct effects on the cardiovascular system that are advantageous during cardiac surgery. Hyperoxia induces vasoconstriction.(1) This results in an increase in systemic vascular resistance (SVR) that may help counter the problem of CPB-associated vasoplegia.(9) High arterial oxygen levels may also decrease heart rate, which is often desirable in patients with at-risk myocardium.(9) Although a reduction in cardiac stroke index has been reported with hyperoxia, there is good evidence that this effect is secondary to an increase in SVR alone and is not indicative of specific myocardial depression.(10) Hyperoxia also causes vasoconstriction at the level of the coronary arteries.(11) Physiologic autoregulation influences coronary arteriolar tone to match myocardial oxygen demand with blood oxygen delivery.(12) Vasoconstriction is an expected physiological response to the increased blood oxygen content under hyperoxic conditions and works to maintain appropriate oxygen delivery to match metabolic demands.

During the reperfusion phase of CPB, after the aortic cross-clamp has been removed and coronary perfusion reinitiated, the myocardium is particularly vulnerable to ROS-mediated damage, a phenomenon known as ischemia -reperfusion injury. In order for a reperfusion injury to occur, it must be preceded by a period of ischemia. If hyperoxia during CPB increases oxygen delivery to tissues and diminishes the ischemic insult, then the impact of reperfusion may be negated. Stated another way, there can be no reperfusion injury if there is no ischemia to begin with.(7)

Gaseous microemboli generated during cardiac surgery are a significant cause of end-organ injury. Increased numbers of microemboli have been shown to be associated with both postoperative acute kidney injury and cognitive dysfunction.(13),(14) The mechanism by which systemic

hyperoxia has the potential to reduce the number of microemboli in circulation is via enhanced denitrogenation. For example, emboli containing an air mix of 80% nitrogen have a lifespan about 10 times longer than those containing 100% oxygen. (15)

A neuroprotective effect from cerebral preconditioning with hyperbaric hyperoxia was demonstrated in humans during on-pump CABG surgery in a randomized controlled trial by Alex and colleagues.(16) The benefit of intraoperative hyperoxia during cardiac surgery is becoming more apparent as cerebral oximetry monitoring with near-infrared spectroscopy becomes more prevalent. There is a growing body of evidence linking cerebral desaturation events during cardiac surgery to increased adverse outcomes, including cognitive decline and increased length of hospital stay.(17) Of particular concern is that these events may be occurring even when peripheral oxygen saturation is within a range that conventionally is expected to provide adequate tissue oxygenation.(18) Early interventional studies aimed at improving clinical outcomes by reducing the length and magnitude of cerebral desaturation show promise. Murkin and colleagues randomized 200 CABG patients to either intraoperative cerebral oximetry monitoring with an intervention protocol for cerebral desaturation below 75% of baseline or standard care blinded to cerebral oximetry data.(19) Patients treated according to the cerebral desaturation protocol had significantly less major organ morbidity and mortality than patients in the standard care group. Increasing the FiO_2 and consequent PaO_2 was an established part of the protocol for treating desaturations in this study.

Patients undergoing cardiac surgery are at significant risk of postoperative pulmonary complications, and these complications may increase morbidity and mortality and lead to prolonged intensive care unit and hospital length of stay.(20) The incidence of postoperative pulmonary complications is increased in patients with intrinsic respiratory disease, asthma, chronic obstructive pulmonary disease (COPD) and heavy smokers.(21) pulmonary complications manifest early as hypoxemia, pneumonia, acute respiratory distress syndrome, and tracheal re-intubation.(22) Adverse neurological outcomes, such as delirium, stroke, and seizure, are frequent as well.(23) There is current debate concerning the link between hyperoxia during cardiac surgery and non-cardiovascular outcomes. Osama Abou-Arab and colleagues performed a post hoc analysis of the Impact of Hyperoxia During Cardiopulmonary Bypass to assess postoperative pulmonary and neurological outcomes during the first 15 postoperative days.(24) The CARDIOX study was a bicentric randomized study assessing two levels of oxygenation (standard care with PaO_2 <150 mmHg vs interventional care with FIO_2 1.0) during CPB. Hyperoxia during CPB did not increase neurological (delirium, seizure, or stroke) or pulmonary complications (postoperative pneumonia or tracheal re-intubation). The authors concluded, that because oxygen delivery is fundamental for positive clinical outcomes, physicians should not be afraid of using supraphysiological concentrations of oxygen. In their retrospective cohort study Kempton and colleagues demonstrated a significant trend between average intraoperative PaO_2 and perioperative CVA (Cerebrovascular accidents), with CVA risk declining with increasing PaO_2. Higher PaO_2 was not demonstrated to be associated with increased risk of post-operative adverse outcomes including pneumonia, prolonged ventilation, perioperative myocardial infarction or cardiac arrest, sternal wound infection, sepsis or renal failure.(25). The recent randomized trial tested the primary hypothesis that intraoperative normoxia, as compared to hyperoxia, reduces postoperative cognitive dysfunction in older patients having cardiac surgery.(26) In this RCT, intraoperative normoxia did not reduce postoperative cognitive dysfunction when compared to intraoperative hyperoxia in older patients having cardiac surgery. Although the optimal intraoperative oxygenation strategy remains uncertain, the results indicate that intraoperative hyperoxia does not worsen postoperative cognition after cardiac surgery.

Unlike in patients undergoing on-pump coronary artery bypass grafting, hemodynamic instability is very common in patients undergoing off-pump coronary artery bypass grafting (OPCABG) because the beating heart with considerable coronary artery disease is lifted, rotated, and fixated during surgery.(27) Supra-physiologic level of PaO_2 may offset the reduced oxygen delivery (DO_2) during OPCABG. Frequent and sustained displacement and restraint of the heart during OPCABG may further necessitate adequate oxygen therapy. PaO_2 has been of less interest because its theoretical contribution to DO_2 and arterial oxygen content (CaO_2) is limited according to the following equation: $DO_2 = CO \times CaO_2 = CO \times (1.34 \times Hb \times SaO_2 + 0.0034 \times PaO_2$.(28) Jae-Woo Ju and colleagues hypothesized that a mild supra-physiologic level of oxygen tension (mild hyperoxia) would improve post- operative mortality in patients undergoing OPCABG.(29) The authors investigated the relationship between intraoperative oxygen tension and mortality after OPCABG. A mildly hyperoxic level of intraoperative arterial oxygen tension was associated with improved outcomes after OPCABG when compared to normoxic, near-normoxic, and severely hyperoxic levels. Patients with intraoperative time-weighted average PaO_2 levels between 150 mmHg and 250 mmHg had a significantly lower risk of in-hospital mortality than those with PaO2 < 150 mmHg and PaO2 > 250 mmHg. It was demonstrated that postoperative mortality may differ according to intraoperative PaO_2 strata given similar Hb concentrations and cardiac output (CO). Dissolved oxygen (or PaO_2) may contribute to DO_2 more than expected in real-world practice. CO levels were comparable between the normoxia/near-normoxia and mild hyperoxia groups, whereas the CO level in the severe hyperoxia group (PaO_2 > 250 mmHg) was lower than that in the other groups. These findings are concordant with previously mentioned RCT(6), that mild hyperoxia (PaO_2 of 150–250 mmHg) increased SvO_2 without a decrease in CO. Recently, Nam and colleagues published the multicenter, cluster-randomized trial (CARROT) that tested the effects of a high FiO_2 on clinical outcomes in patients undergoing OPCABG.(30) The authors compared clinical outcomes

and hemodynamic parameters between patients who received 80% and 30% oxygen during OPCABG. Intraoperative administration of 80% oxygen or 30% oxygen did not affect hospital LOS after OPCABG. The incidence of postop AKI was significantly higher in the FiO_2 0.3 group than in the FiO_2 0.8 group (30.7% vs 19.4%; P = 0.036). The FiO_2 0.8 group also had a significantly greater average cerebral regional SO_2 than the FiO_2 0.3 group (56% vs 52%; P = 0.002). Intraoperative SvO_2 was significantly higher in the FiO_2 0.8 group (74% vs 64%; P < 0.001. the authors concluded, that DO_2, interrogated by SvO_2, may increase to a clinically significant degree as FiO_2 is increased during cardiac surgery, and the increase of SvO_2 is not related to Hb concentration. Although it failed to reduce hospital LOS, an intraoperative FiO_2 of 0.8 provided tissue oxygenation with superior hemodynamics without any worse outcome related to hyperoxia.

Our research article about the effect of FiO_2 on pulmonary gas exchange during OPCABG has been recently published in the journal "Georgian medical news".(31) The aim of our study was to assess PaO_2/FiO_2 ratio, P(a-Et)CO_2 gradient and $PEtCO_2/PaCO_2$ ratio changing while ventilating patients with different FiO_2 during off-pump coronary artery grafting operations. We tried to answer the question, how higher FiO_2 could worsen pulmonary gas exchange during OPCABG and if it might have a significant effect on the outcomes such as hemodynamic and laboratory data, duration of postoperative mechanical ventilation and ICU length of stay. We found, that FiO_2 0.8 was associated with more derangements of pulmonary gas exchange compared with FiO_2 0.5 in patients undergoing sevoflurane anesthesia during OPCABG. The patients ventilated with FiO_2 0.8 had more P(a-Et)CO_2 gradient, less $PEtCO_2/PaCO_2$ ratio and less PaO_2/FiO_2 ratio at the end of OPCABG operations compared with the patients ventilated with FiO_2 0.5. Although FiO_2 did not have an impact on the outcomes we studied, using FiO_2 0.5 seems to be safer in patients undergoing OPCABG.

Recently has been published study protocol of ongoing randomized controlled international multicenter observer-blinded trials that prospectively evaluates the influence of higher inspired oxygen fractions on early postoperative respiratory and oxygenation outcomes in cardiac surgery patients using cardiopulmonary bypass.(32) There is also another randomized clinical trial not finished yet: "The Risk of Oxygen during Cardiac Surgery (ROCS) trial".(33) The investigators randomized 200 elective cardiac surgery patients to receive physiologic or hyper-oxygenation during surgery to test the hypothesis that intraoperative physiologic oxygenation decreases the generation of reactive oxygen species, oxidative damage, and postoperative organ injury compared to hyper-oxygenation. The results of these clinical studies will greatly contribute to finding answers to important questions about the use of oxygen in cardiac surgery.

Conclusion

Supra-physiologic level of PaO_2 may be successfully used in cardiac surgery. Avoidance of mild to moderate hyperoxia in cardiac surgery is not translated into improved clinical outcomes. If such level of PaO_2 is achievable with moderate FiO_2, then there will be no need of using higher FiO_2 during operations to avoid sequential pathophysiologic pulmonary changes accompanied with high inhaled oxygen concentration.

Avoidance of hyperoxia is likely to be of most benefit during the reperfusion phase after resumption of pulsatile flow to ischemic tissue beds. On the other hand, use of hyperoxia during periods of poor tissue perfusion might be beneficial compared with normoxia. Thus, future trials could target hyperoxia in the pre-bypass period and while on CPB to limit ischemia and then target normoxia during reperfusion to reduce exacerbation of subsequent ROS-mediated reperfusion injury.

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