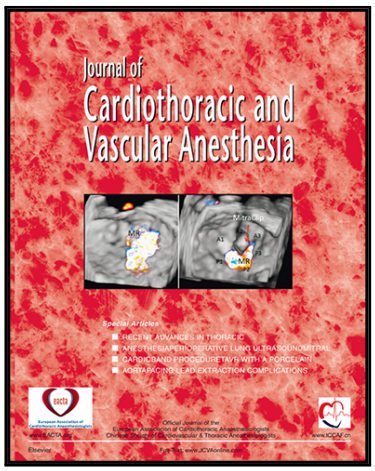

Hyperoxia – a wolf in sheep's clothing?

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PII: S1053-0770(18)31181-9
DOI: https://doi.org/10.1053/j.jvca.2018.12.024
Reference: YJCAN 5049

To appear in: *Journal of Cardiothoracic and Vascular Anesthesia*

Please cite this article as: Dominik P. Guensch MD , Jan-Oliver Friess MD , Balthasar Eberle MD, PhD , Gabor Erdoes MD, PhD , Hyperoxia – a wolf in sheep's clothing?, *Journal of Cardiothoracic and Vascular Anesthesia* (2018), doi: https://doi.org/10.1053/j.jvca.2018.12.024

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Statement of funding: none

Declaration of interest: none

Acknowledgements: none

Keywords: hyperoxia; coronary artery disease; Oxygenation-Sensitive Cardiovascular Magnetic Resonance

In acute medicine, transient hyperoxia is not generally perceived to be detrimental, with many of us clinicians even feeling on the safe side when administering supplemental oxygen.[1] However, evidence is mounting that hyperoxia, especially in the presence of significant coronary artery disease (CAD), may not be benign at all.[2]

In recent years, studies have been emerging which suggest negative effects of administration of supraphysiologic oxygen concentrations, especially in patients with acute myocardial ischemia.[3] As a consequence, the European Society of Cardiology (ESC) has readjusted her guidelines for oxygen therapy in patients with acute coronary syndromes or myocardial infarction. In 2015, ESC recommended administration of supplemental oxygen in NSTEMI only to patients with a peripheral oxygen saturation (SpO_2) of less than 90% or if in respiratory distress.[4] With accruing evidence about the detrimental potential of hyperoxia, ESC has reconfirmed her stance in 2017 for STEMI and now advises, as a "Do-not-do" recommendation (Class III Evidence Level B), against routine administration of supplemental oxygen to patients with acute myocardial infarction if SpO2 is 90% or higher.[5]

Adverse effects of hyperoxia have also been found in patients at much lesser cardiac risk. The Danish PROXI trial compared laparotomies undergoing either a conservative oxygen regime (inspiratory oxygen fraction, FiO_2 of 0.8) or a restrictive one (FiO_2 of 0.3), and found increased long-term mortality following peri-operative hyperoxia.[6] One of their post-hoc analyses reported an incidence of new acute coronary syndrome of 2.5% in the conservative oxygen group vs. 1.3% in the restrictive group.[7] The long-term risk of myocardial infarction was also increased in the conservative group (HR 2.86; 1.10–7.44; p=0.03). This suggested

again, as in the AVOID trial,[3] that perioperative or peri-interventional hyperoxia may adversely affect cardiovascular health even over prolonged periods of time.

Hyperoxia is known to be a potent coronary vasoconstrictor.[8] Hyperoxia-induced blood flow reduction in the left anterior descending coronary artery was reproducibly observed in animal research when employing novel cardiac MRI techniques such as Oxygenation-Sensitive Cardiovascular Magnetic Resonance (OS-CMR) Imaging.[9] In this study, regional myocardial de-oxygenation was observed during hyperoxia only downstream of significant coronary artery stenosis. Also, this was accompanied by impaired contractility of the myocardial segments subtended by the stenosed vessel, whereas contractility of healthy myocardium remained unaffected.

In human studies, hyperoxia (arterial oxygen tension of more than 250 mmHg) has been found to reduce cardiac output by 10–15% in both healthy volunteers and patients with CAD or heart failure.[10] Such studies into animal models and human CAD indicate that a decrease in ejection fraction or stroke volume under hyperoxic conditions can be attributed to depressed myocardial contractility in post-stenotic segments. In patients with chronic stable multi-vessel CAD, who were inhaling supplemental oxygen while undergoing OS-CMR imaging, myocardial de-oxygenation occurred in segments subtended to a significant stenosis and was followed by reduction in diastolic strain rate and prolongation of time-to-peak strain.[11] Both phenomena are very early responses in the ischemic sequence. However, they did not occur uniformly in all individuals of this study. Only approximately 50% of these CAD patients showed worsening of tissue oxygenation, ejection fraction and cardiac output, whereas the other half showed respective improvement.

Thus, in patients with stable CAD or lesser cardiovascular risk who undergo non-cardiac surgery it remains unclear who may benefit from a supraphysiologic oxygen tension and who may not. Weighing in as a potential benefit, hyperoxia has been reported to reduce the incidence of postoperative surgical site infection (SSI) in several but not all randomized controlled trials on this topic.[12] Although such effects were seen almost exclusively in colorectal and other abdominal surgery, the World Health Organization (WHO) has recommended very recently that each and every adult undergoing surgery with general anaesthesia should receive an FiO_2 of 0.8 during the intraoperative and early post-operative period, in order to prevent surgical site infections.[13] Practitioners of cardiovascular anaesthesia now face the dilemma, which of the various guidelines to follow in their patients, which are often at risk of both myocardial ischemia and SSI. In a survey of clinical routine in the UK, an FiO_2 of 0.5 appeared to be standard intraoperative practice, which clearly differs from the recommendation of the WHO, but also from other recommendations to use FiO_2 of 0.3.[14]

Despite a growing number of high-quality studies into pros and cons of applying high FiO_2 in patients with known CAD or at risk thereof, current evidence remains insufficient for definite conclusions. Patients adapt quite variably throughout the course of CAD, and thus show heterogeneous responses to vasoactive stimuli such as hyperoxia[11] and hypercapnia[15]. Even in patients with treated CAD, distal microvascular dysfunction may still be present and may contribute to adverse events during general anaesthesia. Randomized perioperative and long-term outcome studies in well-defined cohorts are therefore needed.

In order to improve perioperative management, there is also a need to better characterize modifiers of myocardial tissue oxygenation and the impact of perioperative interventions. Echocardiography is sensitive for functional sequelae of myocardial ischemia or infarction.

Even wall motion and strain abnormalities, however, occur relatively late in the ischemic sequence of events, followed by ECG changes and rise in serologic biomarkers. Preceding changes of the myocardial tissue oxygen balance can be detected non-invasively with OS-CMR, and this is feasible in most patients who do not have contraindications for MRI scans.[15,16] So far, CMR studies remain a time- and resource-intensive modality, which are not performed routinely. As a perspective for the future, however, OS-CMR may become a valuable tool to assess potential triggers of perioperative myocardial injury in patients at risk, with hyperoxia prominently among them.

In the future, anaesthesia practice will very likely apply individualized oxygen regimes depending on patients' co-morbidities. This is already clinical routine today for selected diseases and patient groups (e.g., colorectal surgery, pulmonary arterial hypertension, or for prevention of retinopathy of prematurity, hypoplastic left heart syndrome, bleomycin-induced lung fibrosis etc.). More evidence is required to apply similar concepts to other cardiovascular diseases, which are more prevalent in daily anaesthesia practice. Future research using novel technologies will identify patient characteristics to help us individually tailor oxygen tension targets and thus reduce adverse outcomes.

Until such evidence helps us to predict, which patient benefits from supraphysiologic oxygen concentration and who does not, cardiovascular patients should be titrated to normoxemia. At any rate, we must look closer who´s under the sheep's clothing.

References

1. Moradkhan R, Sinoway LI: Revisiting the Role of Oxygen Therapy in Cardiac Patients. J. Am. Coll. Cardiol. 56:1013–6, 2010

2. Farquhar H, Weatherall M, Wijesinghe M, et al: Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am. Heart J. 158:371–7, 2009

3. Stub D, Smith K, Bernard S, et al: Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation 131:2143–50, 2015

4. Roffi M, Patrono C, Collet J-P, et al: 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur. Heart J. 37:267–315, 2016

5. Ibanez B, James S, Agewall S, et al: 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur. Heart J. 39:119–77, 2018

6. Meyhoff CS, Jorgensen LN, Wetterslev J, et al: Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. Anesth. Analg. 115:849–54, 2012

7. Fonnes S, Gögenur I, Søndergaard ES, et al: Perioperative hyperoxia - Long-term impact on cardiovascular complications after abdominal surgery, a post hoc analysis of the PROXI trial. Int. J. Cardiol. 215:238–43, 2016

8. McNulty PH, King N, Scott S, et al: Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. Am. J. Physiol. Heart Circ. Physiol. 288:H1057-1062, 2005

9. Guensch DP, Fischer K, Shie N, et al: Hyperoxia Exacerbates Myocardial Ischemia in the Presence of Acute Coronary Artery Stenosis in Swine. Circ. Cardiovasc. Interv. 8:e002928, 2015

10. Smit B, Smulders YM, van der Wouden JC, et al: Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. Crit. Care Lond. Engl. 22:45, 2018

11. Guensch DP, Fischer K, Yamaji K, et al: Effects of hyperoxia on myocardial oxygenation and function in multi-vessel coronary artery disease. J. Cardiothorac. Vasc. Anesth. 32:S61–2, 2018

12. Wenk M, Van Aken H, Zarbock A: The New World Health Organization Recommendations on Perioperative Administration of Oxygen to Prevent Surgical Site Infections: A Dangerous Reductionist Approach? Anesth. Analg. 125:682–7, 2017

13. Allegranzi B, Zayed B, Bischoff P, et al: New WHO recommendations on intraoperative and postoperative measures for surgical site infection prevention: an evidence-based global perspective. Lancet Infect. Dis. 16:e288–303, 2016

14. Morkane CM, McKenna H, Cumpstey AF, et al: Intraoperative oxygenation in adult patients undergoing surgery (iOPS): a retrospective observational study across 29 UK hospitals. Perioper. Med. Lond. Engl. 7:17, 2018

15. Fischer K, Yamaji K, Luescher S, et al: Feasibility of cardiovascular magnetic resonance to detect oxygenation deficits in patients with multi-vessel coronary artery disease triggered by breathing maneuvers. J. Cardiovasc. Magn. Reson. 202018, 2018

16. Luu JM, Friedrich MG, Harker J, et al: Relationship of vasodilator-induced changes in myocardial oxygenation with the severity of coronary artery stenosis: a study using oxygenation-sensitive cardiovascular magnetic resonance. Eur. Heart J. Cardiovasc. Imaging 15:1358–67, 2014