CHAPTER 1
GENERAL INTRODUCTION
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Oxygen (dioxygen, \(O_2\)) is a cornerstone of human life. This highly reactive molecule is used during cellular respiration, which generates the energy required to drive cellular function, repair and growth. Without sufficient oxygen supply, the body resorts to less sufficient forms of energy generation, which are quickly exhausted. However, although oxygen deficiency is undeniably detrimental, an excess of oxygen may be harmful as well.

Physicians often increase the fraction of inspired oxygen (FIO\(_2\)) in patients to prevent or relieve hypoxia due to respiratory or circulatory failure. Because hypoxic patients evidently benefit from oxygen supplementation, oxygen is associated with a general sense of “the more the better” and is regularly administered copiously to be “on the safe side”. Oxygen supplementation is one of the most common medical interventions to date, particularly in acute, perioperative and intensive care medicine; The British Thoracic Society guideline for oxygen use in adults in healthcare and emergency settings advises immediate administration of high-concentration oxygen to critically ill patients and recommends a target arterial haemoglobin oxygen saturation (\(S_aO_2\)) of 94-98% for all patients with acute illness\(^2\,3\). The World Health Organisation recommends the use of 80% oxygen perioperatively to prevent surgical site infections and the United States Centers for Disease control endorses the use of an ‘increased’ FIO\(_2\) in the perioperative period\(^4\,5\). Although there are no oxygen administration guidelines for the intensive care unit (ICU), it has long been common practice to routinely administer at least 40% oxygen to patients receiving mechanical ventilation\(^6\,7\). There is little evidence in support of the existing guidelines, which are mostly based on expert opinions, small studies with severe methodological limitations or data from very specific patient populations (e.g. patients with an exacerbation of COPD).

Fortunately, results of rigorous prospective randomized controlled trials investigating optimal oxygenation targets for specific types of patients are finally starting to emerge\(^8\,12\).

What are the known hazards of excessive oxygen administration? Delivering high concentrations of inspired oxygen, i.e. at a percentage above 60%, for an extended period of time (>24 hours) may lead to inflammation of lung tissue\(^13\,14\). Nevertheless, such high FIO\(_2\)S are sometimes necessary to maintain sufficient oxygen concentrations in arterial blood due to...
pulmonary- or circulatory pathology. However, when more oxygen is given than required for the correction of hypoxia, or when hypoxia was not initially present, the oxygen concentration in arterial blood will rise beyond physiological levels (hyperoxia). Hyperoxia has direct effects on the cardiovascular system, which develop within minutes\textsuperscript{15}. As the oxygen level in blood rises, hyperoxic vasoconstriction and a reduction of the cardiac output occur, which may subsequently impair blood flow to organs. These hemodynamic changes induced by oxygen are less well known among healthcare professionals.

Hyperoxic vasoconstriction has been described in several organs, including the myocardium, brain and retina\textsuperscript{16–18}. A significant reduction of organ perfusion is undesirable because it hampers the supply of oxygen and nutrients, as well as the disposal of waste materials, which both negatively affect organ function. Oxygen is primarily transported via haemoglobin inside erythrocytes. A negligible amount of oxygen is dissolved in plasma and is measured as the partial pressure of oxygen in arterial blood (P$_a$O$_2$). Haemoglobin saturation (S$_a$O$_2$) largely depends on the P$_a$O$_2$. In healthy individuals breathing air, P$_a$O$_2$ will be 75-100 mmHg (10-13.5 kPa) with an S$_a$O$_2$ of 95-100%. Because it is impossible to saturate haemoglobin beyond 100%, further increases in P$_a$O$_2$ induced by supplemental oxygen will only increase the dissolved amount of oxygen, but hardly augment the total oxygen content of blood. Considering that the reductions in blood flow are related to P$_a$O$_2$, rather than oxygen content, hyperoxia has the potential to reduce overall oxygen delivery to organs, rather than enhance it.

Besides these potential negative effects, hyperoxia may also be beneficial. Oxygen is used as a substrate by leukocytes to produce antimicrobial reactive oxygen species (ROS)\textsuperscript{19}. Hyperoxia therefore theoretically supports innate host-defence against microorganisms, which is valuable to prevent surgical site infections or during treatment of sepsis\textsuperscript{20}. Hyperoxic vasoconstriction could also counteract hypotension, reducing the need for vasopressor support\textsuperscript{21,22}. In addition, hyperoxic vasoconstriction may not be present in all vascular beds, leading to a redistribution of blood flow to vital organs such as the intestines, liver and kidney\textsuperscript{22–26}. Nevertheless, much is still unclear, such as the relation between the degree of hyperoxia and hemodynamic changes, whether the changes are similar for all types of patients and if the described effects are clinically relevant.
Clinical trials and retrospective analyses of clinical data show varying results of hyperoxia on clinically relevant outcomes such as mortality and organ function. The results of the first prospective trials show increased mortality in patients with hyperoxic oxygenation targets\textsuperscript{8-10}. In the intensive care population, retrospective data show that 20-50\% of the patients are exposed to hyperoxia\textsuperscript{7,27,28}. In these patients, the relation between P\textsubscript{a}O\textsubscript{2} and mortality appears to follow a U-shape: mortality increases as the P\textsubscript{a}O\textsubscript{2} becomes either unphysiologically low or high\textsuperscript{27,28}. Surprisingly, the nadir of the curve is located in the moderate hyperoxic range. A similar trend in mortality is observed in patients after cardiac arrest\textsuperscript{29-31}. The U-shape suggests the presence of an optimal oxygenation range and that outcomes depend on the magnitude of hyperoxia. Retrospectively, extreme hyperoxia increased mortality in patients after cardiac arrest, whereas moderate hyperoxia was associated with improved organ function\textsuperscript{31}. Similar results were obtained in studies with patients after traumatic brain injury, where negative outcomes (e.g. mortality) were primarily found in the extreme upper and lower P\textsubscript{a}O\textsubscript{2} ranges\textsuperscript{32,33}. Although these data are observational and the underlying mechanisms are unclear, some data thus suggest that presence of moderate hyperoxia may be beneficial.

It is currently unclear via which molecular pathway(s) oxygen exerts its effects on the cardiovascular system. Over the course of million years of evolution, the human body has developed several mechanisms to adapt to acute or chronic tissue hypoxia, such as increasing local blood flow or producing additional red blood cells. Unlike hypoxia however, hyperoxia is an unnatural occurrence and does not exist without human intervention. It is therefore unlikely that the response to hyperoxia underwent the same evolutionary trial and error and may thus produce undesirable side effects. High oxygen concentrations may promote the generation of ROS \textit{in vivo}\textsuperscript{34} and contribute to oxidative stress. ROS are harmful for tissue and can affect the bioavailability of vasoactive substances, such as nitric oxide and prostaglandins, leading to vasoconstriction\textsuperscript{35}. Oxygen may also enhance ROS driven ischemia-reperfusion injury, which is especially undesirable in the case of cardiac arrest, myocardial infarction or cardiac surgery. Due to their short lifespan, ROS are difficult to measure. Clinical studies must resort to measuring secondary messenger molecules in blood, such as F2-isoprostanes, or molecules reflecting
oxidative injury which frequently lack specificity and/or sensitivity. Animal models are more suitable to investigate molecular pathways, because they allow the use of precise and invasive methods. Next to the clinical studies in this work, we therefore also incorporated pre-clinical (animal) studies.

Because both the magnitude and mechanism(s) of hyperoxia-induced hemodynamic alterations are unclear, it is difficult to judge the consequences of the cardiovascular effects of hyperoxia on clinical outcomes. Especially the relation between the degree of hyperoxia and the extent of these effects needs further examination before recommendations can be made for optimal oxygenation targets.

**AIM**
The general aim of this dissertation is to assess the clinical effects of different oxygenation targets during and after cardiac surgery and appraise the effects of hyperoxia on the macro- and microcirculation.
OUTLINE
Following this general introduction, Part I describes studies on the effect of hyperoxia on hemodynamic parameters in patients and healthy volunteers. In chapter 2, we provide an overview of the existing literature on the use of hyperoxia during cardiac surgery. This chapter summarises the safety of high perioperative oxygen targets for cardiac patients and elaborates on the possible molecular mechanisms affected by hyperoxia.

Chapter 3 describes the results of a randomised controlled clinical trial in which patients scheduled for coronary artery bypass graft surgery were allocated to either near-physiological or moderate-hyperoxic oxygen targets during and after surgery. The aim of this study was to determine whether the lower oxygenation targets would reduce myocardial damage and oxidative stress and improve hemodynamics and organ function.

In chapter 4, we describe the dose-response relationship between hyperoxic arterial oxygen tensions, systemic oxygen delivery and changes in the sublingual microcirculation in a group of healthy volunteers.

There is broad consensus in the literature that hyperoxia has hemodynamic consequences. However, the type and severity of the reported effects vary. In chapter 5, we systematically review and analyse the effect of hyperoxia on systemic hemodynamic parameters and oxygen delivery as reported in studies with healthy volunteers and patients with cardiovascular disease or sepsis.

In Part II of this dissertation, the focus shifts to effects of hyperoxia on arteriolar diameter in animals. In chapter 6, we examined hyperoxia-induced changes in vascular tone of isolated arteries from healthy mice using pressure myography. Chapter 7 provides an overview and meta-analysis of the literature on hyperoxic vasoconstriction in various animal species and vascular beds.

Part III is dedicated to the synthesis of the studies presented in this dissertation. In chapter 8, we summarize and discuss the most important findings and provide directions for future investigations. In chapter 9, a lay summary is given in Dutch.
CHAPTER 1

REFERENCES

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