VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine

Institute of Clinical Medicine, Clinic of Anesthesiology and Intensive Care

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INTEGRATED STUDY MASTER'S THESIS

Oxygen: Friend or Foe

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Vilnius, 2026

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STRUCTURE

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ABBREVIATIONS

Abbreviation	Definition
O2	Oxygen
CO2	Carbon dioxide
pO2/ PaO2	Oxygen partial pressure/ arterial partial pressure of O2
SaO2	Arterial oxygen saturation
SpO2	Pulse oximetry oxygen saturation
FiO2	Inspiratory fraction of O2
mmHg	Millimeters of mercury
ARDS	Acute respiratory distress syndrome
CaO2	Arterial oxygen content
HbO2	Oxyhemoglobin
COPD	Chronic obstructive pulmonary disease
ICU	Intensive care unit
ATP	Adenosine triphosphate
NADH+ (H+)	Nicotinamide adenine dinucleotide (+ hydrogen)
FADH2	Flavin adenine dinucleotide
ROS	Reactive oxygen species
Acetyl-coA	Acetyl-coenzyme A
pH	Potential of hydrogen
DNA	Deoxyribonucleic acid
DAMPs	Damage-associated molecular patterns
NO	Nitric oxide
CPR	Cardiopulmonary resuscitation
AED	Automated external defibrillator
ROSC	Return of spontaneous circulation
ERC	European Resuscitation Council
PCAS	Postcardiac arrest syndrome
STEMI	ST-segment elevation myocardial infarction
CK	Creatine kinase
MRI	Magnetic resonance imaging
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
qSOFA	Quick sequential organ failure assessment
bpm	Beats per minute
Il-10	Interleukin 10
MSOD	Multiple system organ dysfunction
TNF alpha	Tumor necrosis factor alpha
CABG	Coronary artery bypass grafting
CSA-MOD	Cardiac surgery-associated multiorgan dysfunction
BBB	Blood-brain barrier
CPAP	Continuous positive airway pressure
iNO	Inhaled nitric oxide
BPD	Bronchopulmonary dysplasia
VEGF	Vascular endothelial growth factor
EOP	Encephalopathy of prematurity
ROP	Retinopathy of prematurity
IGF-1	Insulin-like growth factor 1

1 SUMMARY

Oxygen is essential for human survival, but its therapeutic use remains controversial in critical care settings. While oxygen supplementation is a cornerstone of critical care, its optimal dosage in specific clinical scenarios such as post-resuscitation therapy, sepsis management, cardiac surgery, and critically ill newborns remains unclear. Both hypoxia and hyperoxia can lead to detrimental patient outcomes by causing cellular damage and oxidative stress. The aim of this literature review is to evaluate the effect of oxygen therapy. The subsequent question is concerned with the variation in treatment requirements for these four different critical care settings. The aim is to develop practical treatment recommendations.

Cardiac arrest causes sudden cessation of circulation, resulting in a lack of oxygen supply to the entire body. Restoration of the blood flow and oxygen supply is essential for the ischemic tissue. But a related increase in reactive oxygen species formation is concomitant with enhanced cellular damage and destruction. Studies recommend a controlled reoxygenation after return of spontaneous circulation with saturation targets of 94 to 98% to avoid consequences of hyperoxia.

Sepsis describes a dysregulated host response to infection with hallmarks of hypotension, hypoxia, and life-threatening organ dysfunction. Oxygen therapy aims to address impaired microcirculation and increased metabolic demands. On the one hand, animal research showed that moderate hyperoxia can enhance immune response and reduce bacterial growth during sepsis. On the other hand, clinical trials with septic patients depict an increased risk of organ dysfunction and mortality in patients administered supranormal oxygen values above 97%. From recent clinical evidence, it can be concluded that saturation targets should be kept between 88 and 95%.

In cardiac surgery, especially those requiring cardioplegia, adequate blood supply is a major challenge. In this case a cardiopulmonary bypass machine is used to either provide isolated pulmonary or cardiopulmonary support. The venovenous extracorporeal membrane oxygenation takes over the lung's function of gas exchange while the venoarterial access additionally supports blood circulation. Oxygen therapy is used to improve tissue oxygenation and reduce ischemic injury associated with heart surgery. However, clinical trials could not verify any difference in organ function between patients receiving physiological oxygen saturation compared to hyperoxic supplementation. It can be inferred that it is safe to follow the conservative oxygen strategy since oxygen supplementation seems to play only a marginal role in the cause of postoperative organ failure.

The focus of neonatology lies in the care of sick newborns and preterm infants, defined as a birth before the 37th week of gestation. The immature development leads to adjustment disorders as well as increased sensitivity to diseases and their treatment. Although oxygen titration to hyperoxic

conditions enhances survival rates postnatally, it induces tissue and vascular damage to certain organs. Careful regulation of oxygen saturation is one measure that can be taken to reduce the risk of neonatal pathologies.

SANTRAUKA

Deguonis yra būtinas žmogaus išgyvenimui, tačiau jo terapinis naudojimas intensyviosios terapijos sąlygomis tebėra ginčytinas. Nors gydymas deguonimi yra intensyviosios terapijos pagrindas, jo optimali dozė konkrečiose klinikinėse situacijose, pvz., po gaivinimo, gydant sepsį, širdies chirurgijoje ir kritiškai sergančius naujagimius, tebėra neaiški. Tiek hipoksija, tiek hiperoksija gali sukelti žalingą paciento būklę, sukeldamos ląstelių pažeidimus ir oksidacinį stresą. Šios literatūros apžvalgos tikslas – įvertinti deguonies terapijos poveikį. Kitas klausimas susijęs su gydymo reikalavimų skirtumais šiose keturiose intensyviosios terapijos srityse. Tikslas – parengti praktines gydymo rekomendacijas.

Širdies sustojimas sukelia staigų kraujotakos nutrūkimą, dėl kurio visam kūnui trūksta deguonies. Kraujo tėkmės ir deguonies tiekimo atkūrimas yra būtinas išeminiams audiniams. Tačiau su tuo susijęs reaktyviųjų deguonies formų susidarymas, sukeliantis padidėjusį ląstelių pažeidimą ir irimą. Tyrimai rekomenduoja kontroliuojamą reoksigenaciją po savaiminės kraujotakos atsigavimo, siekiant 94–98 % prisotinimo, kad būtų išvengta hiperoksijos pasekmių.

Sepsis apibūdina sutrikusią organizmo reakciją į infekciją. Jam būdinga hipotenzija, hipoksija ir gyvybei pavojinga organų disfunkcija. Deguonies terapija yra skirta sutrikusiai mikrocirkuliacijai ir padidėjusiam metabolizmui gydyti. Viena vertus, tyrimai su gyvūnais parodė, kad vidutinė hiperoksija gali sustiprinti imuninį atsaką ir sumažinti bakterijų augimą sepsio metu. Kita vertus, klinikiniai tyrimai su sepsio pacientais rodo padidėjusią organų disfunkcijos ir mirtingumo riziką pacientams, kuriems buvo skirta didesnė nei 97 % deguonies koncentracija. Remiantis naujausiais klinikiniais duomenimis, galima daryti išvadą, kad deguonies prisotinimo lygis turėtų būti išlaikomas tarp 88 ir 95 %.

Širdies chirurgijoje, ypač kai reikalinga kardioplegija, tinkamas kraujo tiekimas yra didelis iššūkis. Šiuo atveju naudojamas širdies ir plaučių šuntavimo aparatas, skirtas izoliuotam plaučių arba širdies ir plaučių palaikymui. Venoveninė ekstrakorporinė membraninė deguonies sistema perima plaučių dujų mainų funkciją, o venoarterinė prieiga papildomai palaiko kraujotaką. Deguonies terapija naudojama audinių deguonies tiekimui pagerinti ir su širdies operacija susijusiam išeminiam pažeidimui sumažinti. Tačiau klinikiniai tyrimai negalėjo patvirtinti jokio organų funkcijos skirtumo tarp pacientų, kuriems buvo skiriamas fiziologinis deguonies prisotinimas, ir pacientų, kuriems buvo skiriamas hiperoksinis papildymas. Galima daryti išvadą, kad saugu laikytis konservatyvios

deguonies strategijos, nes deguonies papildymas, atrodo, turi tik nežymų poveikį pooperaciniam organų nepakankamumui.

Neonatologija daugiausia dėmesio skiria sergantiems naujagimiams ir neišnešiotiems kūdikiams, t. y. gimusiems iki 37 nėštumo savaitės. Nesubrendęs vystymasis sukelia adaptacijos sutrikimus, taip pat padidėjusį jautrumą ligoms ir jų gydymui. Nors deguonies titravimas iki hiperoksinių sąlygų padidina išgyvenamumą po gimimo, jis sukelia tam tikrų organų audinių ir kraujagyslių pažeidimus. Kruopštus deguonies įsotinimo reguliavimas yra viena iš priemonių, kurių galima imtis siekiant sumažinti naujagimių patologijų riziką.

2 KEYWORDS

Oxygen, resuscitation, sepsis, cardiac surgery, neonatology

3 METHODOLOGY

A systematic literature review was conducted with PubMed as the primary database. MeSH terms related to the subtopics such as oxidative stress, hyperoxia, cardiac surgery, and bronchopulmonary dysplasia were applied as a search strategy. The inclusion criteria comprised clinical trials, meta-analyses, and systematic reviews published mainly within the past ten years. Articles were only used if they provided, among others, a representative sample size and relevant outcome measures. Through a critical evaluation of experimental and clinical data, this study aims to summarize the current state of research and recent guidelines of oxygen therapy, while also highlighting gaps and controversies. The objective of this thesis is to delineate practical recommendations for optimal oxygen levels that will have a beneficial effect in the aforementioned clinical settings.

4 INTRODUCTION

Oxygen (O2) is a gas indispensable to life for all aerobic organisms, including humans. The lung assures the supply of oxygen for the organism. Its main function is gas exchange via diffusion across the blood-air barrier, in particular the uptake of O2 and the disposal of carbon dioxide (CO2). This process is dependent on efficient ventilation, which allows the exchange of air in the lung by inspiration and expiration. Since O2 is the most important electron acceptor in biochemical reactions, it is essential for the energy production inside the cells. Because humans are incapable of storing O2

efficiently, a constant supply is necessary. The pathophysiology of respiratory insufficiency can be caused by a disturbance of one or more of the following subprocesses of gas exchange: ventilation, diffusion, perfusion, or distribution. Under such circumstances, O2 therapy might become necessary to prevent severe injury to organs.

The beginning of oxygen therapy dates back to the 18th century, where it was rarely known and more connected to mysticism. It was said to heal many different diseases, but the reputation of O2 therapy was rather bad due to diverse side effects. During the following decades, three main obstacles retarded the usage of O2 therapy. Firstly, the pathophysiology of many diseases, and therefore the indications, was unclear. Secondly, the production of liquid O2 was very complicated and cost intensive. And thirdly, it was impossible to archive accurate dosing (1). It was only at the beginning of the 20th century that O2 became a well-established treatment, as techniques were developed to overcome these obstacles.

Since then, O2 therapy is widely used for treatment of variable conditions that cause O2 levels to drop. There are two distinct terms to describe the state of low oxygen depending on the location. Hypoxia describes the condition of low tissue oxygenation. Whereas hypoxemia delineates a state of low O2 in arterial blood.

O2 therapy is commonly used to address hypoxemic hypoxia. Hypoxemia is evaluated on the basis of partial pressure of O2, the pressure that is exerted by O2 on the arterial wall (pO2), or the oxygen saturation (SaO2) in arterial blood. SaO2 is measured non-invasively at peripheral capillaries via pulse oximetry (SpO2) or invasively via an arterial blood gas analysis from an arterial line (SaO2). The value of pO2 can depict a disturbance in gas exchange in the lung, not a change in hemoglobin concentration or erythrocyte function. To evaluate if an impairment of oxygenation occurs, the ratio of arterial pO2 to fraction of inspired oxygen (FiO2) can be calculated. Under physiological conditions this so-called Horowitz index (PaO2/FiO2) would be 350-500 mmHg. Any values below 300 mmHg indicate a respiratory failure like in ARDS. Hypoxia is best evaluated by calculating the cardiac output times the arterial O2 content. The arterial O2 content consists of the O2 fraction bound to hemoglobin as well as the fraction dissolved in plasma. The value is called arterial oxygen content (CaO2) (2).

O2 therapy is based on the assumption that a high FiO2 allows a sufficient oxygenation of arterial blood despite decreased pulmonary function. The oxygen-hemoglobin dissociation curve at figure 1 (Amboss, 2024) shows the association between the arterial oxygen saturation (HbO2) as a function of O2 partial pressure (pO2). The high pO2 pressure in the lung allows efficient saturation of hemoglobin and cannot be improved by further increase in pO2. In contrast, the pO2 in peripheral tissue is relatively low, thus allowing the release of O2 from hemoglobin. Due to the sigmoidal shape of the curve, a decrease of pO2 would not cause a linear drop in the binding affinity for O2. A drop from, for example, 90 to 75 pO2 mmHg corresponds with a decrease of HbO2 to 94%, which would not have pathological consequences for the body. Whereas a further decrease in pO2 would cause the HbO2 saturation to decline much quicker, leading to hypoxia. This condition is addressed by O2 therapy with the aim to increase the arterial pO2 to preferably normal values of 65-100 mmHg. The higher the partial pressure, the lower the hemoglobin binding affinity for O2, thus allowing increased O2 dissociation and tissue oxygenation (3), (4), (5).

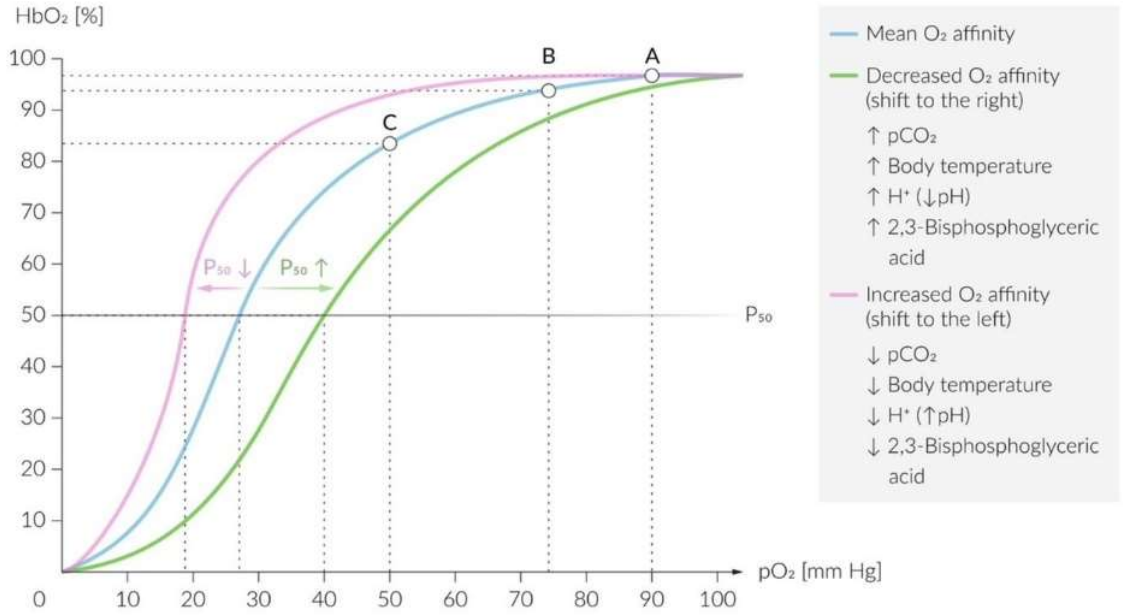


Figure 1. Oxygen-hemoglobin dissociation curve

It is known that a pronounced lack of O2 leads to severe organ damage, primarily of the brain. What is not yet known is the exact value below which hypoxia is harmful to humans (6). In particular, patients in the ICU require O2 therapy, as many critical illnesses induce hypoxemia. Critical illness is defined as a state of vital organ dysfunction and impending death. Pathologies that require organ support, including O2 supplementation, are, for example, brain injury, sepsis, or acute coronary syndrome. Even though critically ill patients with hypoxia are more likely to die than those with

normoxia, it often remains unclear whether the increased mortality is due to the lack of O2 or due to the disease itself. Nowadays O2 therapy is strictly regulated by law and defined indications. However, there is insufficient data on the effectiveness of O2 treatment for many diseases, especially for patients with an SpO2 level of >90%. Another issue with O2 therapy is that the aftereffects of hyperoxemia occur later and are often less obvious than those of hypoxia (6).

The following section discusses the pathophysiology of oxygen toxicity provoked by iatrogenic oxygen supplementation. This is followed by the question whether oxygen therapy holds more harm or benefit at certain clinical conditions. In other words, Oxygen – friend or foe? The focus will be on the clinical situations of resuscitation from cardiac arrest, sepsis, cardiac surgery, and neonatology. I have chosen these pathologies due to the fact that they are part of everyday practice in hospitals and still hold a high risk of mortality.

5 OXYGEN – WHEN PHYSIOLOGY BECOMES PATHOLOGY

Under physiological conditions, energy in the form of ATP is produced in the mitochondria by oxidizing the reduction equivalents NADH+H+ and FADH2. This respiratory chain is shown in figure 2 (Amboss, 2023) and consists of an electron transport chain, which allows the release of electrons from NADH+H+ and FADH2 and oxidative phosphorylation. It is responsible for ATP production. In each case two electrons combine with two protons and half a molecule of oxygen to form water (complex IV). The energy that is produced thereby is used to synthesize ATP in a process called oxidative phosphorylation (8).

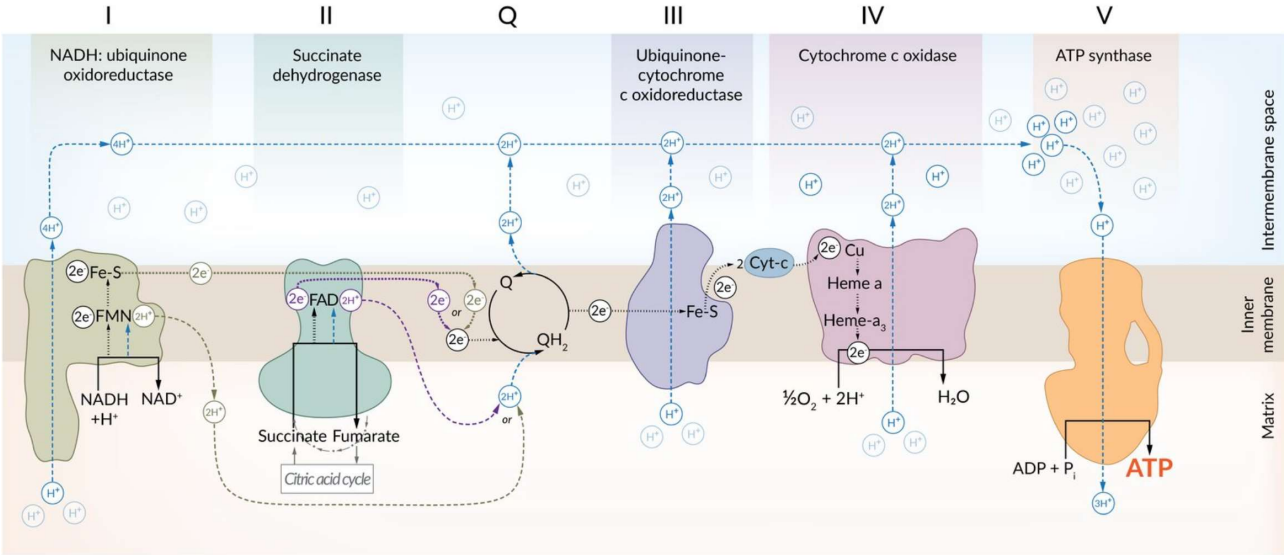


Figure 2. Respiratory chain

If the transfer of electrons to oxygen gets disturbed, oxygen molecules with unpaired electrons in their orbitals are formed. They are called oxygen radicals or reactive oxygen species (ROS). Free radical formation can be a result of exogenous or endogenous events. In general, the respiratory chain

of mitochondria makes up the main source of ROS production in the cell. In the following, I will focus on ischemia as an endogenous source of ROS. The term ischemia encompasses any condition causing decreased blood supply and therefore decreased oxygen supply to the cells. As oxygen is unavailable as a terminal electron acceptor in these circumstances, the cells use an alternative method to regenerate NAD+ for glycolysis. This process is called anaerobic glycolysis. Glucose gets converted to pyruvate, but instead of transforming it to acetyl-CoA which could be used in the citric acid cycle, lactate is formed. Although the lactic acid cycle yields less energy, it allows glycolysis to continue with the resulting NAD+ as oxidant. Lactate normally gets converted to pyruvate again (9). At hypoxia this alternative ATP production becomes problematic because it causes an overproduction of lactate in the ischemic tissue, resulting in accumulation of lactate in the blood serum. An example for such a state of hypoperfusion would be septic shock (10). Metabolic acidosis with a blood pH of <7,35 arises. Because the electron transport chain at the mitochondria is disrupted during hypoxia, mitochondria themselves get impaired. This results in the formation of ROS and a decreased production of ATP. Severe cellular damage not only occurs during ischemia but especially at reperfusion of the previously ischemic areas, a process known as reperfusion injury. The reperfusion supplies mitochondria with oxygen again, resulting in reactivation of the electron transport chain. The released electrons will react with the preexisting free radicals, thereby increasing the amount of ROS. Besides, reperfusion triggers an inflammatory reaction. Endothelial cells at the previous ischemic environment get activated which will provoke the release of ROS by leukocytes or granulocytes. Apart from the new formation of ROS, their clearance by antioxidants, for example via enzymes like glutathione-peroxidase, may also be impaired due to a lack of ATP during ischemia. ROS are highly reactive and tend to fill their orbitals, thus reacting with many cellular biomolecules which leads to cell structure damage. Subsequently, an imbalance of the cellular homeostasis causes damage to cell structures like proteins, lipids, or nuclei acid, which initiates apoptosis and necrosis of the cell. The permeability of the cellular and mitochondrial membranes is increased, leading to cellular edema. DNA and mitochondrial DNA get damaged, thus causing a vicious cycle because the now dysfunctional mitochondria also produce a high amount of ROS (11). Injured or dying cells release endogenous damage-associated molecular pattern molecules (DAMPs) that activate the innate immune system, for example, by being recognized by neutrophils. They in turn initiate inflammation and organ injury. Activated cells from the innate immune system also produce ROS with the consequence of further tissue damage (12). Additionally, ROS alter the microvasculature in two different ways. Firstly, the permeability increases, resulting in tissue edema. Secondly, they cause the transition of nitric oxide (NO), which is an important vasodilator, to peroxynitrite. This results in a

reduced availability of NO and, consequently, vasoconstriction. The microcirculation gets impaired. The effects of ROS are summarized in figure 3 (Singer et al., 2021, page 2).

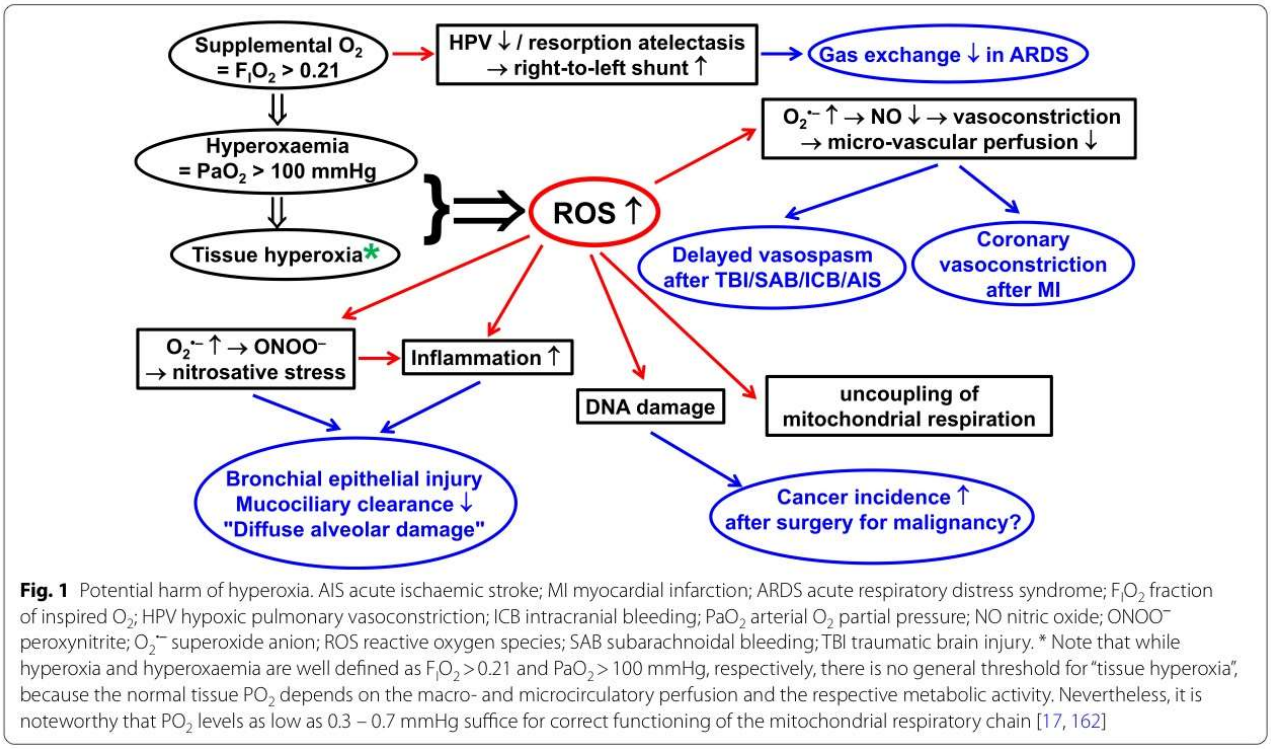


Fig. 1 Potential harm of hyperoxia. AIS acute ischaemic stroke; MI myocardial infarction; ARDS acute respiratory distress syndrome; F_IO_2 fraction of inspired O_2; HPV hypoxic pulmonary vasoconstriction; ICB intracranial bleeding; PaO_2 arterial O_2 partial pressure; NO nitric oxide; $ONOO^-$ peroxynitrite; $O_2^{\bullet-}$ superoxide anion; ROS reactive oxygen species; SAB subarachnoidal bleeding; TBI traumatic brain injury. * Note that while hyperoxia and hyperoxaemia are well defined as $F_IO_2 > 0.21$ and $PaO_2 > 100$ mmHg, respectively, there is no general threshold for "tissue hyperoxia", because the normal tissue PO_2 depends on the macro- and microcirculatory perfusion and the respective metabolic activity. Nevertheless, it is noteworthy that PO_2 levels as low as 0.3 – 0.7 mmHg suffice for correct functioning of the mitochondrial respiratory chain [17, 162]

Figure 3. Potential harm of hyperoxia

This state of increased concentration of ROS is called oxidative stress. It can be assumed that not O2 itself but ROS cause toxic effects. To overcome the disadvantages of ROS overproduction, different mechanisms of elimination exist. These so-called antioxidants can either prevent their formation, for example, the protein ceruloplasmin, or remove ROS by enzymes, for example, glutathione peroxidase or vitamin C or E. Moreover, ROS may function as mediators to induce autophagy of the cell. Thereby cellular components get recycled during oxidative stress.

ROS production increases with both O2 deficiency and excess. Iatrogenic hyperoxia will develop, for instance, under two circumstances: either the amount of inhaled O2 increases, e.g., at O2 supplementation with FiO2 of >0.21, or during the process of reperfusion or reoxygenation of organs. Consequently, under both circumstances, the formation of ROS rises (13). Oxygen toxicity is caused by the augmented formation of free radicals and the subsequent exhaustion of the antioxidant system due to the fact that the antioxidant system is impaired. This occurs, for example, during critical illness and mechanical ventilation.

Two organ systems that are affected the most by the adverse effects of ROS are the central nervous system and the respiratory system. Given that neurons are very sensitive cells, the CNS is usually affected first. Manifestations of neurotoxicity encompass, among others, seizures, nausea, and visual

disturbance. In the lungs, cell death provokes interstitial pulmonary edema and thus, impaired gas exchange. Additionally, a 100% O2 supply causes a nitrogen washout from the lungs. Nitrogen normally makes up around 78% of air in the alveoli. Since it naturally serves as a support to keep alveoli open, a displacement of it with O2 induces a pressure drop inside the alveoli because O2 quickly diffuses into the blood. The consequence is the formation of absorption atelectasis because more gas is absorbed from the alveoli than the amount of gas entering it. It results in a ventilation-perfusion mismatch, which in turn will provoke hypoxia and dyspnea. Oxygen toxicosis is especially prominent under conditions of prolonged exposure and hyperbaric airway pressure. Apart from that, the vascular resistance will rise during arterial hyperoxia, resulting in vasoconstriction. Especially the brain and the heart are particularly vulnerable to hypoxia. The consequence of a hypoxic heart would be a decline in heart rate and stroke volume and therefore cardiac output (12).

6 OXYGEN THERAPY IN FOUR CLINICAL SITUATIONS - RESUSCITATION FROM CARDIAC ARREST

Cardiac arrest is defined as the sudden stop of cardiac function and blood circulation, which quickly leads to death due to the cessation of tissue oxygenation. The etiology can be subdivided into primary and secondary etiologies, with primary cardiac pathologies like coronary heart disease being the most common cause in adults. Cardiopulmonary resuscitation (CPR) has to be initiated as soon as possible to artificially maintain circulation and ventilation until cardiac function is re-established. Basic life support by non-medical first aiders is focused on CPR with thirty chest compressions and two rescue breaths per cycle plus usage of an automated external defibrillator (AED). Advanced life support by health care workers complements resuscitation medications, advanced airway management, and potential treatment of reversible causes of cardiac arrest. The administration of 100% O2 via bag valve mask is an inherent part of advanced resuscitation. In respiratory insufficiency, expressed by hypoxemia and hypercapnia, supraglottic airway devices like laryngeal mask airways can be used. Endotracheal intubation with an endotracheal tube becomes necessary to prevent aspiration at impaired consciousness with an extenuated or absent gag reflex.

The return of spontaneous circulation (ROSC) is evidenced by a palpable pulse or measurable blood pressure. During this phase the aim is to give optimal hemodynamic support, treat the cause of cardiac arrest, and minimize secondary brain injury. According to the guidelines of the European Resuscitation Council (ERC) from 2021, an advanced airway, if possible tracheal intubation, should be established. The titration of inspired oxygen is set to an SpO2 of 94-98%. Via ventilation, the pCO2 levels should reach normocapnia (33-45 mmHg) (14). Even if ROSC is achieved, only around 40% will survive to hospital discharge (15). The high mortality is associated with the post-cardiac arrest syndrome (PCAS), a reaction to successful resuscitation and subsequent reperfusion. It

encompasses systemic and organ-specific damage due to ischemia-reperfusion injury (16). Specifically, this can lead to anoxic brain injury, decreased cardiac output, and a systemic inflammatory response. These factors could result in multiorgan failure and vascular damage. It can be exacerbated by preexisting heart diseases and the vasoconstrictive effect of ROS, which are produced during ischemia and reperfusion.

O2 supplementation during the post-ROSC phase seems to play a major role in PCAS. As stated in an article by J. H. Kilgannon et al., even though laboratory data and animal studies showed evidence about the harmful effects of hyperoxia after ROSC, it is not yet sufficiently confirmed by clinical data (17). She and her team conducted a large multi-center cohort study in the USA from 2001 to 2005 to evaluate if hyperoxia, defined as ≥300 mmHg after ROSC in patients admitted to the intensive care unit (ICU), is associated with increased in-hospital mortality. 18% of the 6326 patients investigated had hyperoxia and showed a significantly higher in-hospital mortality (63%) compared with the normoxia group (45%) and the hypoxic group (57%), as recapped in figure 4 (Kilgannon, 2010, page 2160).

Table 4. Outcomes of Study Patients

	All Patients (N = 6326)	Hypoxia (n = 3999)	Normoxia (n = 1171)	Hyperoxia (n = 1156)
In-hospital mortality, No. (%) [95% CI][a]	3561 (56) [55-58]	2297 (57) [56-59]	532 (45) [43-48]	732 (63) [60-66]
Survivors, No. (%)	2765 (44)	1702 (43)	639 (55)	424 (37)
Independent functional status at hospital discharge, No. (%) [95% CI][b]	939 (34) [32-36]	570 (33) [31-36]	245 (38) [35-42]	124 (29) [25-34]
Discharge destination, No. (%)				
Home	1203 (44)	746 (44)	294 (46)	163 (38)
Rehabilitation facility	405 (15)	248 (15)	87 (14)	70 (17)
Nursing home	759 (27)	462 (27)	162 (25)	135 (32)
Transfer to another acute care hospital	91 (3)	64 (4)	13 (2)	14 (3)
Other or unknown	307 (11)	182 (11)	83 (13)	42 (10)

[a] $P<.001$ for both comparison of hyperoxia with normoxia and for hyperoxia with hypoxia.
[b] Defined as able to live at home and requiring no assistance to complete activities of daily living. $P=.002$ for comparison of hyperoxia with normoxia and $P=.10$ for comparison of hyperoxia with hypoxia.

Figure 4. Outcomes of Study patients

The authors assumed this happens on the basis of the oxidative stress initiated by reperfusion. It is further perpetuated by continuously keeping pO2 above physiological values via high FiO2. Other recent clinical data corroborate the Kilgannon study, supporting the thesis that hyperoxia after ROSC could cause more harm than good. Yet the question remains whether the risk of negative outcome depends on a threshold of pO2 or rather a dose-dependent relation. By using a database from Project Impact, Kilgannon et al. conducted a multicenter cohort study to investigate this issue. They included

4459 patients, of whom the average received O2 therapy to a PaO2 of 231 mmHg post-resuscitation. The results clearly show a dose-dependent relation between supranormal pO2 levels and risk of in-hospital death. While a small increase of pO2 of 25 mmHg causes a rise of 6% in risk of death, an increase of 100 mmHg already enhances the mortality risk to 24% (18). Figure 5 illustrates this linear relation (Kilgannon, 2011, page 2720). The O2 supplementation can intensify the reperfusion injury, especially in the brain and heart. Released ROS will enhance inflammation and disturb cellular respiration, thus increasing the risk of in-hospital mortality.

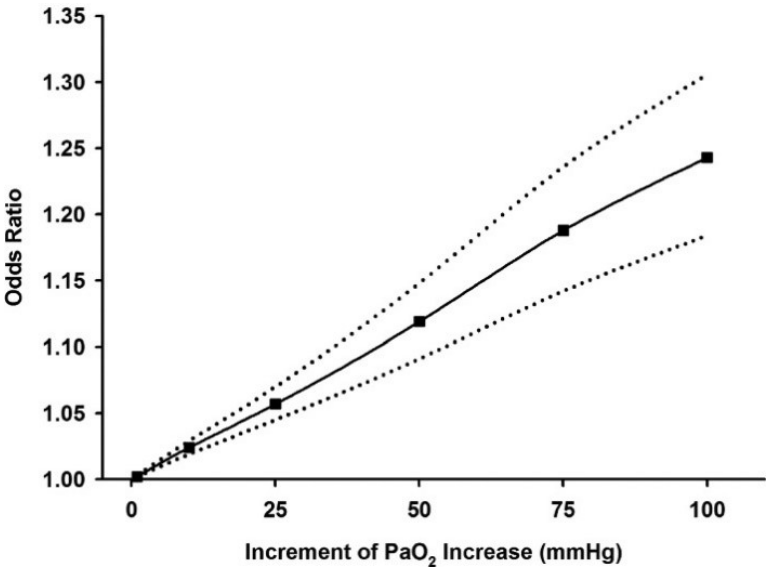


Figure 5. Odds ratio for in-hospital death and associated 95% confidence intervals (dotted lines) for increments of rise in PaO2

An experimental study of Stub et al. focused on the case of ST-segment elevation myocardial infarction (STEMI) (19). The pathology is based on acute ischemia, most commonly due to occlusion of one or more coronary arteries by an atherosclerotic plaque. The consequence of myocardial necrosis can potentially lead to arrhythmias and cardiac arrest. The primary focus of the study was on the impact of oxygen supplementation on the size of myocardial infarction. Patients with STEMI were divided into two groups. One group (49.6%) received 8l/ min of O2. The second group (50.6%) did not receive supplemental O2. To evaluate the primary end point, cardiac enzymes troponin I and creatine kinase (CK) were evaluated up to 72 hours after admission to the hospital, and a cardiac MRI was conducted after six months. One outcome of their study is that withholding O2 supplementation in normoxic STEMI patients has no negative consequences since symptoms like chest pain did not differ compared to the oxygen group. Only 7.7% of the non-O2 group needed supplementation because SaO2 dropped below 94%. Furthermore, O2 therapy increased cardiac damage, evident by increased levels of CK, as shown in figure 6 (Stub, 2015, page 2148) and an augmented infarct size in MRI compared to the other group. Adverse clinical outcomes like recurrent myocardial infarction

or cardiac arrhythmias were set as secondary end points. They were more frequent in the oxygen group (21.9%) than in the control group (15.4%).

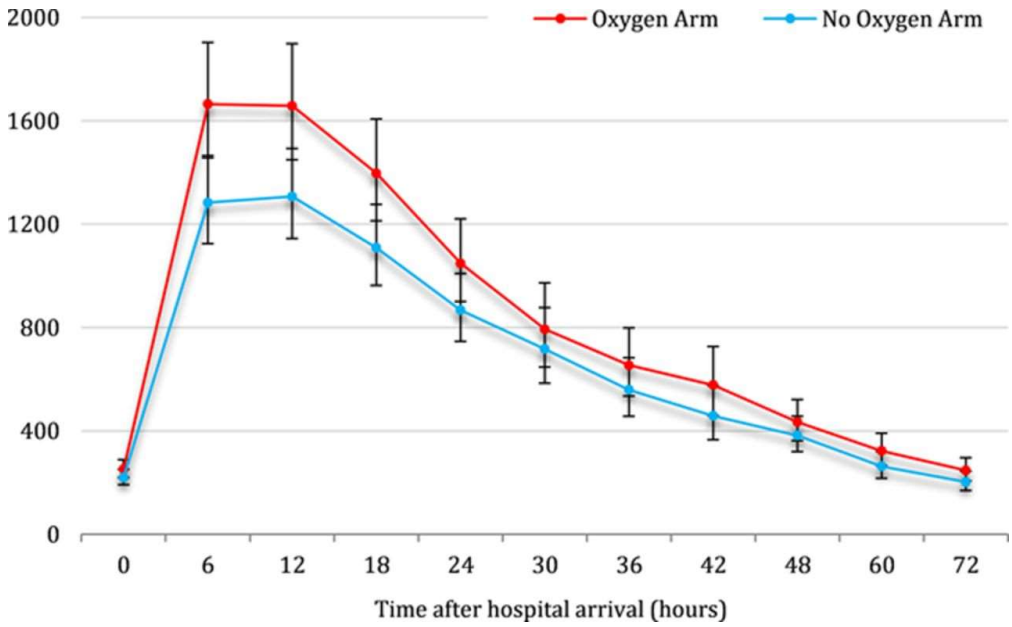


Figure 6. Creatine kinase release (U/L) over 72 hours in patients with confirmed STEMI

These results can be explained by the enhanced formation of ROS at ischemia-reperfusion injury and their alteration of coronary vessels in particular, causing reduced blood flow and increased vascular resistance. To conclude, there was no considerable benefit of routine O2 supplementation but rather aggravated myocardial injury.

The results of the teams of Kilgannon and Stub conclude that hyperoxia as well as hypoxia are harmful in post-ROSC phase and should be avoided. While O2 therapy of 100% FiO2 during CPR helps to achieve ROSC, it should be handled with caution when circulation returned successfully. Clear guidelines on the level of oxygen saturation are still missing. Kilgannon and her colleagues state that clinical trials are needed to test the safety and efficacy of a controlled reoxygenation strategy as part of post-cardiac arrest care. Therefore, the ERC recommends avoiding hyperoxia, applying controlled reoxygenation, and titrating SaO2 to 94-96%.

7 OXYGEN THERAPY IN FOUR CLINICAL SITUATIONS - SEPSIS

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (20). If this is accompanied by severe cellular, circulatory, and metabolic dysfunction, the condition is called septic shock. The imbalance of O2 supply and demand accounts for a major part of the pathophysiology of sepsis. On the one hand, inflammatory mediators alter the microvasculature, causing capillary leak and vasodilation via NO release. On the other hand, the

hyperinflammatory reaction increases the cellular O2 demand, while O2 utilization by mitochondria is disturbed by a lack of O2 and newly formed ROS. The cellular respiration shifts to anaerobic metabolism, causing lactic acidosis. All factors add up to hypoxia and ultimately multiple organ failure.

Since sepsis is a clinical syndrome, its diagnosis cannot be based on a single biomarker, but rather on the systematic screening of critically ill patients. Conditions such as refractory hypotension and increased lactate levels can confirm the suspicion of sepsis. Any source of infection, most commonly bacterial, can induce a dysregulated immune reaction and systemic inflammatory response. Examples of such infections include pneumonia and endocarditis. Main symptoms are an altered mental status, fever, hypotension, tachycardia, and tachypnoea. In addition, organ specific symptoms may occur which provide an indication of the focus of the infection. Sepsis and especially septic shock still have a high mortality of approximately 24-35% (21), depending on the country, which is why it should be diagnosed and treated quickly. Several screening tools, such as SOFA and qSOFA, have been established to detect sepsis and septic shock. Organ dysfunction is present if two or more criteria from either of these scores are met. The sequential organ failure assessment (SOFA) score screens for partial pressure of oxygen compared to fraction of inspired oxygen, platelet count, bilirubin count, mean arterial pressure, Glasgow coma scale and creatinine. The quick SOFA (qSOFA) score is a simplified version of this comprehensive score, focusing only on mental state, systolic blood pressure and respiratory rate. According to the Surviving Sepsis Campaign from 2021 (20) the availability and adherence to hospital guidelines for identification and response has more impact on the survival of septic patients than the type of guideline used. The authors point out the limitations of these screening tools and advise against using qSOFA as the sole screening tool due to its low sensitivity. Additional laboratory diagnostics are used to evaluate the severity of infection, organ dysfunction and for follow-up. The required response within one hour after identifying a septic patient is summarized in the one-hour sepsis bundle. It consists of measuring lactate levels, obtaining blood cultures prior to administration of antibiotics and administration of broad-spectrum antibiotics, crystalloid and vasopressors if needed. Although a pathogen detection is not necessary to diagnose sepsis, the type of antibiotic should be selected according to the presumed focus of infection and the local antimicrobial resistance status. Commonly used antibiotics are piperacillin/tazobactam or ceftazidime. Hypotension is addressed by crystalloid infusion which can be supported by vasopressors like norepinephrine.

As O2 supplementation is thought to improve oxygenation of the cells and increase systemic vascular resistance, it is included in the therapeutic scheme of sepsis. The extent of therapy remains under research. Some experimental animal studies showed an advantage of O2 therapy during infection.

The team of Knighton conducted an experimental study based on the knowledge that granulocytes are dependent on O2 supply for adequate immune response (22). After injecting Escherichia coli into the skin of guinea pigs the animals were treated with different levels of O2. While those guinea pigs who were in a hypoxic environment with 12% O2 showed an increase in the number and size of infected skin areas, those treated with 21% as well as those with 45% O2 had decreased necrotic areas. The same study was conducted a few years later, whereat the investigated outcome was the number of living bacteria at the infected area after O2 supplementation (23). Here as well, in the guinea pigs with moderate hyperoxia, fewer bacteria were detected than in those with hypoxia. According to that, O2 supports the defense of pathogens by leukocytes.

The study of Waisman et al. investigated the effects of different levels of normobaric hyperoxia on septic rats (24). They were divided into three groups receiving no O2, 70%, or 100%. After 48 hours, inflammatory markers were used to evaluate up to which concentration O2 is effective to reduce sepsis. While the rats treated with 70% of O2 showed a spread of leukocytes and macrophages into lungs as well as lung consolidation, the group treated with 100% of O2 did not show an increased tendency to tissue inflammation, as illustrated in figure 7 (Waisman et al., 2012, page 97). It can be concluded that potential benefits of O2 therapy are primarily based on its anti-inflammatory effects, which are of great importance during a state of systemic dysregulated immune response such as sepsis.

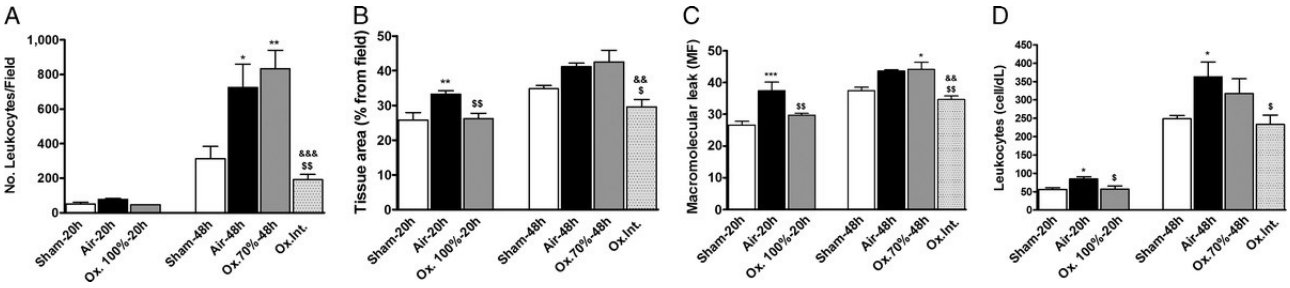


Figure 7. Inflammatory characteristics of remote lung injury following cecal ligation and puncture

A similar approach was taken in the study of Jon Buras and his team in 2006. They conducted an experimental study with sepsis-induced mice treated with hyperbaric oxygen (25). The focus lay on the relationship between O2 and interleukin-10 (Il-10), an anti-inflammatory cytokine. The results showed an increased secretion of IL-10 by macrophages in mice treated with hyperbaric oxygen, with the resulting higher probability of survival. Whereas mice with a genetic deficiency of IL-10 could not profit from the therapy. The researchers assume that hyperbaric oxygen may protect from sepsis mortality via an anti-inflammatory mechanism. Although O2 seems to be beneficial for sepsis in a manner of reduction of inflammation, it is still questioned if these potential benefits outweigh the

disadvantage of the increased ROS production, which is inevitably connected with O2 supplementation.

A study by Rodríguez-González and colleagues from 2014 investigated the effects induced by hyperoxia in an animal model of sepsis (26). Their assumption was that iatrogenic hyperoxia may worsen the organ dysfunction initially triggered by sepsis. As stated by the authors, many septic patients do not die from the infection but from the subsequent multiple system organ dysfunction (MSOD). To investigate this, sepsis was induced in rats by ligating and puncturing the cecum. Thereafter the rats were randomly divided into four groups, which were exposed to either 21%, 40%, 60%, or 100% O2 for 24 hours. The investigated parameters are crucial markers of a dysregulated immune system: the spread of infection into different body fluids, levels of inflammatory biomarkers and ROS, and hematological parameters. They were examined after 24 hours of treatment.

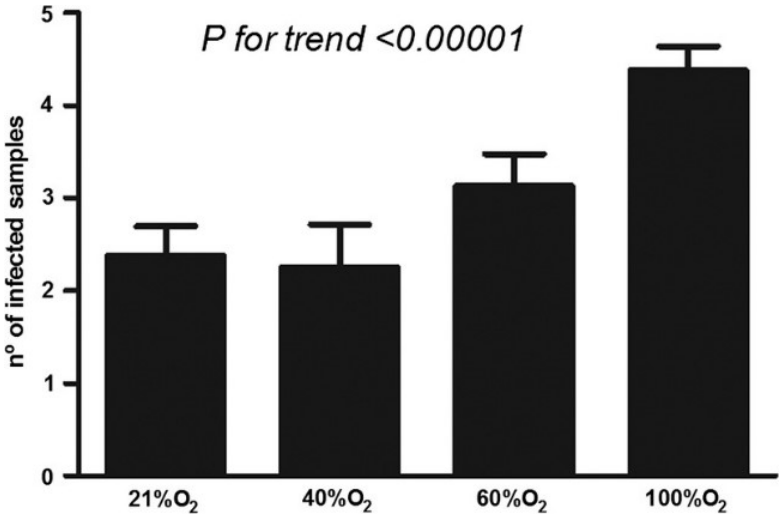


Figure 8. Effects of inspired oxygen on the number of infected samples after experimental sepsis

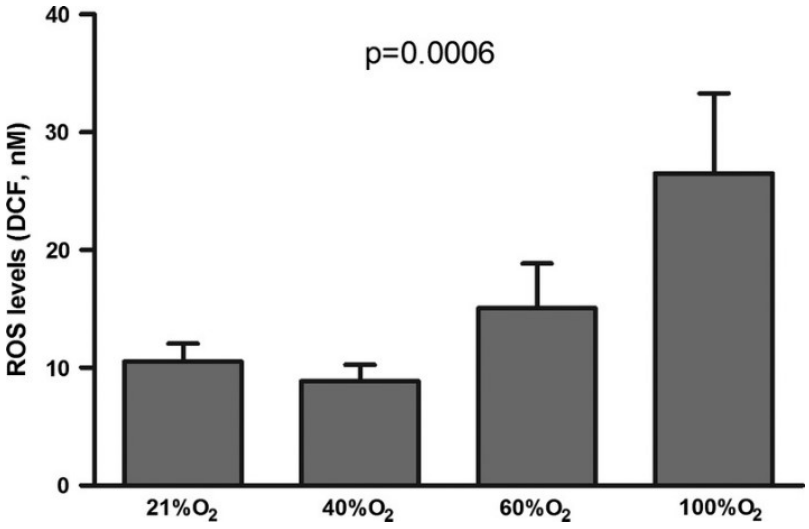


Figure 11. Reactive oxygen species serum levels in septic animals after 24 h of exposure to different oxygen concentrations

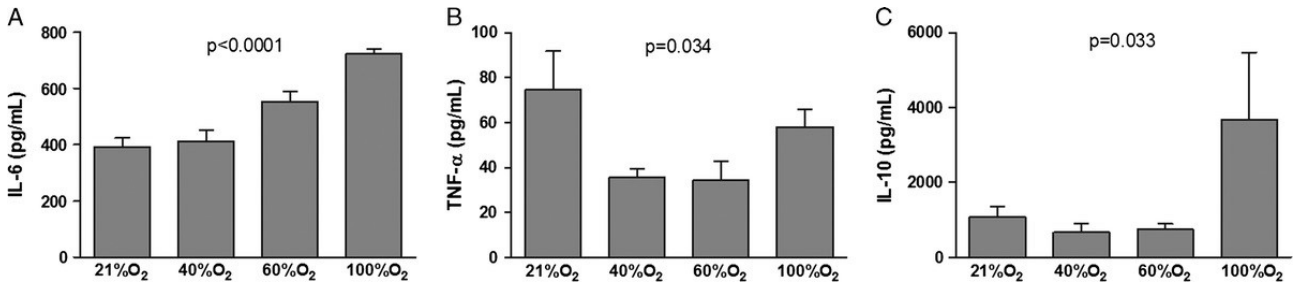


Figure 10. Effects of inspired oxygen concentration on IL-6 (A), TNF-α (B), and IL-10 (C) serum levels in septic rats

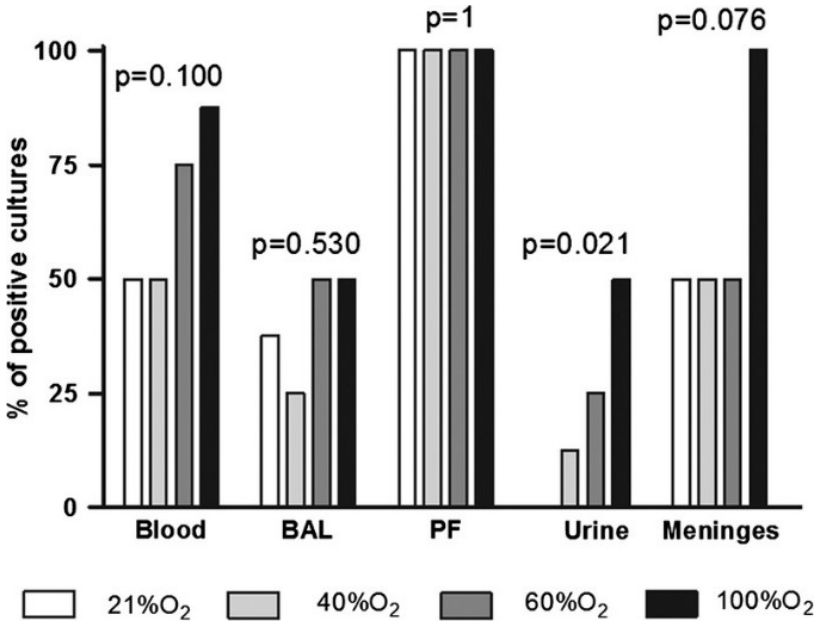


Figure 9. Effects of oxygen on the percentage of positive cultures in different samples analyzed

It is clearly visible from the figures 8-11 (Rodríguez-González et al., 2014, pages 150-152) that an increase in O2 saturation correlates with an increase of inflammatory markers like IL-6, IL-10, and TNF alpha, as well as ROS formation. In particular, the spread of infection appears to be facilitated by 100% O2 supplementation, especially to the urinary and meningeal systems. It can be assumed that oxidative stress provoked by hyperoxia and disbalance between ROS formation and antioxidant activity causes cellular disturbance and therefore organ failure, like in MSOD.

Even though, there are experimental and clinical studies related to O2 therapy during sepsis, the Surviving Sepsis Campaign still states that no recommendations can be made about conservative O2 targets with sepsis-induced hypoxemic respiratory failure (20). Nevertheless, O2 therapy is indicated in septic patients in a state of insufficient oxygenation, aiming for SpO2 of 88-95% (27). The authors of Surviving Sepsis Campaign suggested using a high-flow nasal cannula for administration. According to a Dutch study, ventilated patients in the ICU are often provided with a high fraction of O2 in inspired air, even though hyperoxia is already reached (28). It is known that such high PaO2 values trigger enhanced ROS formation, which results in oxidative stress causing tissue inflammation, for example in the respiratory system.

An Italian research group conducted a study about the outcome of mortality of patients in the ICU, comparing conservative with conventional oxygen therapy (29). In this single-center randomized clinical trial, 434 patients in an ICU in Modena either received O2 therapy to reach 94-98% SpO2 (conservative group, n=216) or allowing SpO2 to reach 97-100% (conventional group, n=218). The primary outcome investigated was the mortality; secondary outcomes covered the development of organ failure and infection at least 48 hours after hospital admission and the need for surgical revision. The outcomes are listed in figure 12 (Girardis et al., 2016, page 5). In summary, the conservative group with O2 targets of 94-98% had better outcomes in terms of ICU mortality and risk of developing shock or sepsis. Even though, the study was terminated early due to lack of enrollment, it can be concluded that a conservative O2 supplementation with PaO2 values below 100 lowers the risk of mortality for ICU patients. Accordingly, PaO2 values of more than 100 are related to higher mortality, increased risk of organ failure, especially of the liver, episodes of shock, and increased incidence of bacteremia.

Table 2. Primary and Secondary Outcomes

	Oxygen Therapy, No. (%)			
	Conservative (n = 216)	Conventional (n = 218)	Absolute Risk Difference (95% CI)	*P* Value
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017 to 0.150)	.01
Secondary outcomes				
Hospital mortality	52 (24.2)	74 (33.9)	0.099 (0.013 to 0.182)	.03
New organ failure during ICU stay	41 (19.0)	56 (25.7)	0.067 (−0.012 to 0.145)	.09
Respiratory failure	14 (6.5)	14 (6.4)	−0.126 (−0.189 to −0.064)	.98
Shock	8 (3.7)	23 (10.6)	0.068 (0.020 to 0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008 to 0.088)	.02
Renal failure	26 (12.0)	21 (9.6)	−0.024 (−0.084 to 0.035)	.42
New infections during ICU stay	39 (18.1)	50 (22.9)	0.049 (−0.027 to 0.124)	.21
Respiratory	30 (13.9)	37 (17.0)	0.031 (−0.038 to 0.099)	.37
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000 to 0.090)	.049
Surgical site[a]	10 (7.2)	12 (9.1)	0.019 (−0.048 to 0.088)	.68
Surgical revision[a]	18 (12.9)	16 (12.1)	−0.008 (−0.088 to 0.073)	.84
Mechanical ventilation–free hours, median (IQR)	72 (35 to 110)	48 (24 to 96)	24 (0 to 46)	.02
ICU length of stay, median (IQR), d	6 (4 to 10)	6 (4 to 11)	0 (0 to 2)	.33
Hospital length of stay, median (IQR), d	21 (13 to 38)	21 (12 to 34)	0 (−5 to 1)	.21

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Only in surgical patients (139 in the conservative group and 132 in the conventional group).

Figure 12. Primary and secondary outcomes

These results correlate with the findings of Rodríguez-González et al., who illustrated an increase in inflammatory markers and ROS in septic rats treated with 100% of O2.

Hyperoxia seems to impede the immune system, which allows infections to spread more easily, ultimately leading to death. This hypothesis is supported by the study of Morrow and her colleagues about how hyperoxia influences the phagocytic function of macrophages encountering Pseudomonas aeruginosa (30). According to their results, macrophages are impaired in fighting the pathogens due to the damaging effect of the augmented ROS.

Another randomized clinical trial investigated the effects of hyperoxia on patients with septic shock. The team of P. Asfar divided mechanically ventilated patients with septic shock into two groups, either administering 100% O2 (n=219) or limiting it to a range of 88-95% (n=223). 28-day mortality was set as the outcome (31). While 43% of the patients in the hyperoxia group died, only 35% in the normoxia group died. Besides, more serious adverse events, such as atelectasis, occurred in the hyperoxia group. Here as well, ROS-related tissue damage is thought to be the reason. The additionally investigated difference between isotonic and hypertonic saline solution showed no significant difference in mortality.

Apart from the immune system, hyperoxia may also alter the vascular system. A systematic review and meta-analysis conducted by Smit and colleagues summarized the results of some studies related

to the question of what kind of effect acute hyperoxia produces on patients with cardiovascular alterations (27). Furthermore, they intended to check the commonly assumed hypothesis that O2 supplementation increases the O2 delivery. Patients with heart failure reacted the most to hyperoxia, as enhanced vasoconstriction raises the afterload of the heart, resulting in decreased cardiac output. Septic patients, however, neither showed increased vascular resistance nor enhanced O2 delivery. This might be due to vasoplegia, a phenomenon of vasodilation and hypotension seen in septic patients with bacterial infection. Therefore, vasopressors and infusions remain crucial therapeutic measures in sepsis. In the studies reviewed in the meta-analysis, no increase in systemic O2 delivery could be detected, neither in patients with sepsis or heart failure nor in healthy volunteers. The authors conclude that the potential benefit of higher O2 concentration in the blood is outweighed by the reduced cardiac output and increased vascular resistance. Hence, supplementation at levels of hyperoxia is not only of no avail but might influence hemodynamics in a negative way, especially for patients with heart failure.

To summarize, the disrupted microvasculature is the main pathology that leads to negative consequences of inadequate O2 therapy for septic patients. Hyperoxia in combination with a hyperinflammatory state causes increased formation of ROS, leading to oxidative stress. Oxidative stress damages cellular membranes, interfering with the physiological function of alveoli and red blood cells, among others. The implications are acute lung injury, atelectasis, thromboembolic events, and disrupted mucosal barrier of the gut. Additionally, the hyperoxia-induced vasoconstriction reduces O2 supply to vital organs like the brain, kidneys, and heart (28).

8 OXYGEN THERAPY IN FOUR CLINICAL SITUATIONS - CARDIAC SURGERY

Surgeries make up a great part of medical practice and can be either diagnostic, curative, or palliative. Surgeries can significantly impact the body's physiological processes. It is assumed that the administration of a supraphysiological concentration of O2 during the intervention can offset some of the negative consequences of surgery. These would be, for example, an extension of the period during which oxygenation is ensured in case of ventilatory failure, a diminution of tissue damage caused by ischemia, or a reduced risk of surgical site infection (29). Contrariwise, hyperoxia raises the concentration of ROS, leading to cellular destruction and vasoconstriction, especially in patients with heart failure (27). An observational cohort study from 2022 detected an association between increased FiO2 of >21% and postoperative organ injury (30). The primary endpoints investigated were acute kidney injury, myocardial injury, and lung injury. Patients administered

supraphysiological O2 had greater odds for all mentioned organ injuries compared to those with physiological O2 saturations. However, they excluded patients who potentially suffered from preoperative or intraoperative myocardial injury.

Cardiac surgery in particular leads to changes in hemodynamics and microvasculature, consequently altering O2 delivery to tissue. Cardiac surgeries comprise valve repair, cardiac implantable electronic devices, or coronary artery bypass grafting (CABG), for instance. The latter can be done with or without using a cardiopulmonary bypass machine. A well-known complication of cardiac surgery is the cardiac surgery-associated multiorgan dysfunction (CSA-MOD). Amongst others, it is based on a systemic inflammatory response, especially during application of a cardiopulmonary bypass (CPB), ischemic-reperfusion injury, micro- or macro-embolism and hemodynamic instability.

Up to now there are no guidelines for the degree of O2 supplementation during cardiac surgery, and variable studies show different results. The research team of J. Wetterslev warns of a lack of evidence of benefits from FiO2 of >60% and potential side effects after conducting a review about hyperoxia during variable surgeries. Diverse studies investigated the impact of hyperoxia on postoperative outcome. The effect of 30% versus 80% FiO2 supplementation on patients undergoing off-pump CABG was examined in a multicenter study including 414 patients in 2023 (31). Although the length of hospital stay was the same for both cohorts, the patients receiving 80% FiO2 had an improved oxygenation in total as well as cerebral oxygenation in particular. Additionally, fewer patients suffered from postoperative acute kidney injury in the cohort with increased FiO2. Following the assumption that hyperoxia compensates for ischemic injury from CPB surgeries, the CARDIOX trial investigated whether a mean PaO2 of 447 mmHg reduced the incidence of postoperative arterial and ventricular fibrillation compared to a standard of <150 mmHg (32). The incidence of adverse cardiovascular events was 30% in both groups; thus, hyperoxia could not improve the outcome. Referring to this, normobaric hyperoxia during coronary artery bypass surgery alters hemodynamic processes to the point of inadequate cardiac output, according to a study by Harten et al. (33). A randomized control trial took the opposite approach by investigating 50 patients to determine whether O2 supplementation close to physiological levels during CABG allows an improvement of cardiovascular function. The results showed no difference in levels of markers for myocardial injury or cardiac function between hyperoxic and near-physiologic treatment groups (34). Additional markers included creatinine and lactate levels to estimate tissue perfusion and organ injury. The values behaved consistently, as shown in figure 13 (Smit et al., 2016, page 6).

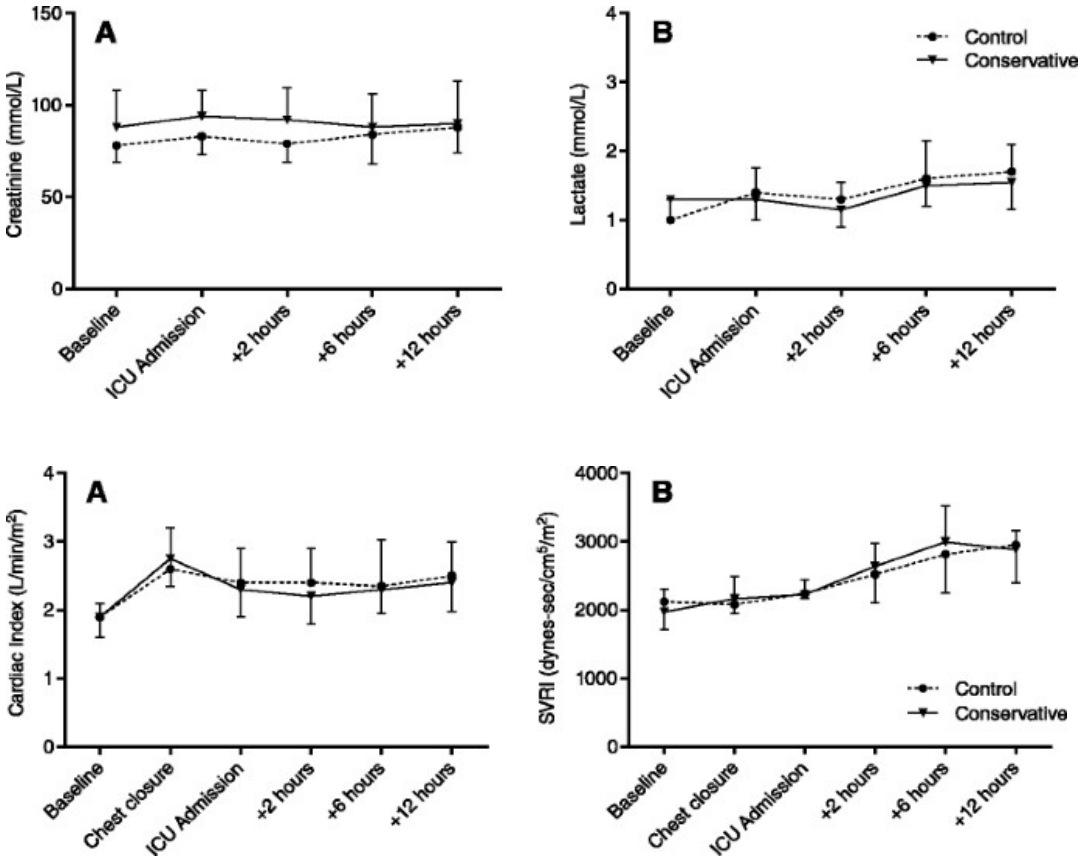


Figure 13. Perioperative markers for tissue injury (upper row) and hemodynamics (lower row)

The authors conclude that although hemodynamics did not improve with the conservative O2 approach, it can be applied safely since no hypoxic events occurred.

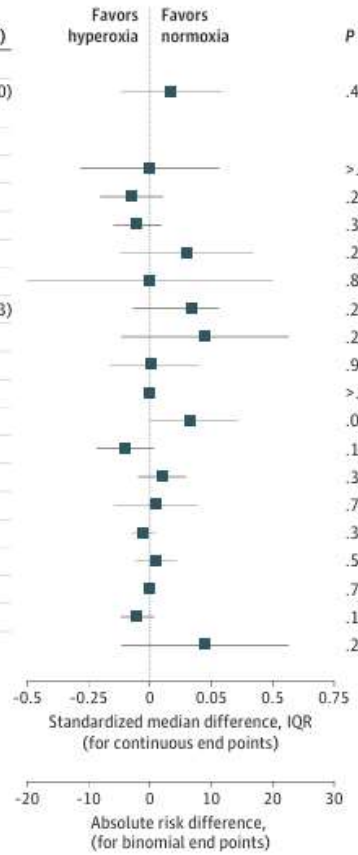
As mentioned before, CSA-MOD is a potential consequence of cardiac surgery and encompasses disturbed function of the kidneys in particular but also the heart, liver, and nervous system. The fact that blood gets in contact with artificial surfaces while traveling through the CPB machine causes variable disturbances. The immune system releases proinflammatory mediators. Mechanical stress of erythrocytes is provoked by CPB as well as blood transfusions, triggering hemolysis. Heme contains reactive iron species that can participate in oxidative reactions and give rise to further ROS (35). This promotes tissue damage and oxidative stress. Additionally, blood returning to the body is oxygenated to supraphysiological levels, which further promotes ROS formation as well as ischemic-reperfusion injury. Those processes are known to contribute to the multiorgan dysfunction. McGuinness and colleagues set up the hypothesis that organ damage and thus length of hospital stay may be reduced by avoiding hyperoxia during cardiopulmonary bypass (36). A total of 298 patients got randomly assigned to receive either O2 supplementation with a PaO2 range of 75-90 mmHg, resulting in a saturation of 97%, or conventional treatment to maintain a saturation of 99% during surgery. The primary outcome investigated was the incidence of cardiac surgery-associated acute kidney injury.

Moreover, markers for organ injury and length of hospital stay were examined. The evaluation revealed no significant difference between the research groups, neither in incidence of kidney injury nor in other events of organ injury or length of stay. The authors conclude that applying FiO2 of 97% during CPB was safe but did not lower the risk of multi organ dysfunction.

A similar approach was taken by the study group of Lopez and colleagues, who conducted a recent randomized clinical trial assessing oxidative stress and organ injury after cardiac surgery by comparing a normoxic with a hyperoxic study group (37). Of 200 patients, half were assigned to FiO2 values of 100%, and the other half to saturations of 97%. Oxidative stress was evaluated by measuring levels of isoprostanes and isofurans during surgery. Changes in organ function were observed for the kidney, heart, and central nervous system. Primary and secondary clinical end points are summarized in figure 14 (Lopez et al., 2024, page 1113).

Figure 3. Clinical Outcomes and Safety Events

Outcome	Median (IQR) Hyperoxia (n = 100)	Normoxia (n = 100)	Difference (95% CI)	*P* value
Primary clinical end point				
Change in serum creatinine from baseline to postoperative day 2, mg/dL	0.01 (−0.12 to 0.19)	−0.01 (−0.16 to 0.19)	0.03 (−0.04 to 0.10)	.45
Secondary clinical end points				
AKI, No. (%)	21 (21)	21 (21)	0 (−11.3 to 11.3)	>.99
AKI (moderate or severe), No. (%)[a]	2 (2)	5 (5)	−3.0 (−8.1 to 2.1)	.25
Dialysis, No. (%)	1 (1)	3 (3)	−2.0 (−5.9 to 1.9)	.31
Delirium, No. (%)	22 (22)	16 (16)	6.0 (−4.8 to 16.8)	.28
Delirium duration, d[b]	2.0 (1.0 to 3.0)	2.0 (1.0 to 2.3)	0 (−1.0 to 1.0)	.83
Delirium severity, CAM-ICU-7 score[c]	0.83 (0.33 to 1.50)	0.79 (0.19 to 1.25)	0.17 (−0.08 to 0.33)	.20
Atrial fibrillation, No. (%)	46 (46)	37 (37)	9.0 (−4.6 to 22.6)	.20
CK-MB postoperative day 1, ng/mL	27.2 (11.5 to 58.3)	24.5 (13.4 to 40.8)	0.2 (−5.9 to 7.3)	.97
Myocardial infarction, No. (%)	0	0	0 (0 to 0)	>.99
Postoperative mechanical ventilation, h	6.2 (4.7 to 9.4)	5.3 (4.2 to 7.6)	0.7 (0 to 1.5)	.06
Reintubation, No. (%)	1 (1)	5 (5)	−4.0 (−8.7 to 0.7)	.10
Pneumonia, No. (%)	3 (3)	1 (1)	2.0 (−1.9 to 5.9)	.31
Surgical site infection, No. (%)	7 (7)	6 (6)	1.0 (−5.8 to 7.8)	.77
Transient ischemic attack, No. (%)	0	1 (1)	−1.0 (−3.0 to 1.0)	.32
Stroke, No. (%)	2 (2)	1 (1)	1.0 (−2.4 to 4.4)	.56
ICU length of stay, d	3.0 (2.0 to 4.0)	3.0 (2.0 to 5.0)	0 (0 to 0)	.76
In-hospital death, No. (%)	0	2 (2)	−2.0 (−4.7 to 0.7)	.15
Composite of organ injury and death, No. (%)[d]	63 (63)	54 (54)	9.0 (−4.7 to 22.6)	.20



Data are presented as medians (IQRs) and absolute median differences (95% CIs) for continuous variables and as counts (percentages) and absolute risk differences (95% CIs) for categorical variables. *P* values were calculated using the Wald and Agresti-Coull methods for median differences and risk differences, respectively. In the Forest plot, we standardized the median difference for continuous variables such that 0.2 units on the risk difference scale represent the difference between the 75th and 25th centiles of the continuous variable. CK-MB indicates creatine kinase–myocardial band, measured the morning of postoperative day 1.

[a]Stage 2 or 3 acute kidney injury (AKI) based on Kidney Disease: Improving Global Outcomes consensus criteria.

[b]Among 38 participants who developed delirium.

[c]Mean confusion assessment method for the Confusion Assessment Method for the Intensive Care Unit 7 (CAM-ICU-7) score over the first 3 postoperative days.

[d]Any of AKI, delirium, atrial fibrillation, myocardial infarction, stroke, transient ischemic attack, pneumonia, surgical site infection, or death.

Figure 14. Clinical Outcomes and Safety Events

During surgery the hyperoxia group showed only a slightly higher increase in markers for oxidative stress compared to the normoxic group. The incidence of acute kidney injury was 21% for both groups. In relation to cognitive dysfunction, the normoxia group had 6% less risk of developing delirium. Other measurements of organ injury showed no significant difference in relation to O2 supply. It can be inferred that although oxidative stress during surgery was increased in hyperoxia patients, the level of O2 seems to have no effect on postoperative organ failure.

Adverse events from cardiac surgery include alterations of microvasculature and hemodynamics. Especially the brain reacts in a sensitive way to such changes. Postoperative delirium occurs in 25% of cardiac surgery patients. The team of Lopez conducted a clinical study with 400 cardiac patients, focusing on the association between intraoperative oxidative damage and postoperative delirium (38). Oxidative stress was evaluated by measuring plasma levels of isofurans and isoprostanes. In addition, the degree of neuronal injury was assessed by monitoring changes in plasma levels of ubiquitin carboxyl-terminal hydrolase isoenzyme L1, an enzyme specific for neuronal damage. The researchers tested the hypothesis that a disturbance of the blood-brain barrier (BBB) influences the relation between oxidative damage and delirium. Plasma S100 calcium-binding protein served as a marker for BBB changes. The incidence of delirium was 27.3%. Patients who developed a delirium showed increased markers of oxidative stress and BBB disruption during surgery compared to patients without a delirium. The results showed an association between oxidative damage and postoperative neuronal injury and delirium. Besides, the inadequate function of the BBB influences the interplay between oxidative damage, neuronal injury, and delirium. The authors conclude that delirium after cardiac surgery may partly be provoked by neuronal injury, which in turn is related to the extent of oxidative damage.

The same conclusion is drawn by a team of researchers in Boston one year later. Shaefi et al. randomly assigned 100 patients aged 65 or older to receive either O2 supplementation with FiO2 values of 0.35 or 0.1 during their CPB surgery. The primary point of investigation was postoperative neurocognition, which was assessed by the Montreal Cognitive Assessment test. The median score reached in both cohorts two days after surgery was 18. The follow-ups during a time period of six months showed no difference as well. Only 55% of patients participated in the neurocognitive test after six months. It can be concluded that O2 supplementation on physiological levels does not help to reduce neurocognitive dysfunction (39). The authors assume that CPB and the resulting systemic inflammatory reaction are of greater importance for ischemic reperfusion injury and adverse events than the arterial oxygen content alone (39).

9 OXYGEN THERAPY IN FOUR CLINICAL SITUATIONS – NEONATOLOGY

The field of neonatology provides medical care to newborns and especially premature infants. The process of birth requires huge adaptation to the extrauterine environment. Given that the body of premature infants is structurally and functionally immature, medical support is needed for successful postnatal transition. Prematurity is defined as a birth occurring between the 20th week and before the 37th week of pregnancy. Extremely preterm are considered those born before the 28th week. Risk factors include fetal causes like chorioamnionitis, multiple gestations, or polyhydramnios, and maternal causes like nicotine abuse, gestational hypertension or diabetes, and previous preterm births. Neonatal resuscitation includes cardiac support with chest compressions, fluid resuscitation, and epinephrine as required (40). The international consensus of neonatal resuscitation from 2015 recommends respiratory support with O2 therapy of 21-30% for preterm neonates <35th gestational week and noninvasive CPAP (continuous positive airway pressure) ventilation for spontaneous breathing infants over invasive ventilation (41). After oxygen therapy was widely used in the delivery room for long time, attention is now drawn towards the risk of oxygen toxicity. While some complications of premature infants, such as neonatal respiratory distress syndrome, arise from immature organ development, others develop as a result of treatment measures, with oxygen supplementation playing a major role.

One reason why premature infants cannot deal well with high oxygen partial pressure is because the fetal organism develops with a PaO2 of about 30 mmHg from the umbilical vein (42). This is possible due to fetal hemoglobin, which predominates during the embryonic, fetal, and newborn periods and allows a higher O2 affinity than adult hemoglobin. The sudden increase in O2 pressure after birth, as well as potential birth asphyxia or perinatal infection, promotes the production of ROS. The oxygen radical defense system is not yet sufficiently developed, resulting in higher sensitivity to oxidative stress (42). Surfactant deficiency disorder additionally diminishes adequate ventilation. The incidence is inversely proportional to the gestational age since surfactant production from type two alveolar cells starts at the 20th week and is not equally distributed within the lung until the 35th week. Thus, the alveolar surface tension in preterm infants is high, leading to alveolar collapse and insufficient gas exchange. This neonatal respiratory distress syndrome is treated with ventilation, positive end-expiratory pressure, and endotracheal surfactant administration. O2 supplementation might be necessary if ventilation is insufficient (43). This raises the question about the adequate amount of O2 supplementation to prevent damage from hypoxia as well as hyperoxia. Guidelines published 2025 by the American Heart Association recommend to orientate oxygen administration on gestational age (44). While late preterm and term born babies should receive 21% of O2 initially, newborns with a

gestational age <35 weeks should receive O2 saturations ranging from 21-30%. The guidelines of the European Resuscitation Council (ERC) of 2025 suggest using 21% O2 for newborns from week 32 onwards. Preterm infants born before week 32 should receive 30% O2 (45). Both guidelines are based on the consensus of the International Liaison Committee on resuscitation (ILCOR) (46). The authors recommend initially titrating O2 to lower levels for a gestational age <35, as no difference in adverse clinical outcomes was observed between the study groups. Further research is needed since the study is based on low evidence. Pulse-oximetry on the right hand preductal and oxygen blenders should be used, physiologically showing SpO2 of >90% ten minutes after term birth (47). A study of Oei et al. points out that only 11% of 706 observed preterm infants achieved 80-85% saturation 5 min postnatally (48). An SpO2 of 21-30% could be inefficient to support reaching required saturation in the other 89% of preterm newborns. The failure to achieve saturation targets was associated with a higher probability of adverse events like intraventricular hemorrhage or bradycardia. Further evaluation is needed to determine if the causality lies in the infant's clinical condition or the O2 therapy. A study by Oei et al. about targeted O2 in resuscitation revealed an increased probability of death for neonates below the 28th week of gestation if they were treated with SpO2 of 21% instead of 100% (49). The authors state that the validity is low because of the underpowered study design. A recent randomized control trial by Sekar et al. investigated the effect of adding NO to inhaled O2 during the first 20 minutes of preterm infant resuscitation. Of the total 28 infants, those receiving iNO had considerably less exposure to high O2 saturation and no increase in adverse events (50).

One of the main pathologies associated with hyperoxia in preterm neonates is bronchopulmonary dysplasia (BPD). This chronic inflammatory disease has a multifactorial etiology with triggers before, during, and after birth. Prenatal risk factors are intrauterine growth restriction and maternal smoking. Natal factors like prematurity and low birth weight show higher incidence. But one of the most crucial risk factors is O2 therapy postnatally (51). Diagnosis is based on typical changes in lung X-rays, like diffuse densities and areas of atelectasis and hyperinflation. The incidence is higher in neonates with lower gestational age and lower birth weight. Since the structural changes of a rise in the number of alveoli and blood vessels and a thinning of the alveolo-capillary barrier occur after the 26th week of pregnancy, preterm infants often lack these crucial adaptations, thus requiring respiratory support. The newer form of BPD is mainly defined by hypoplasia of alveolar structure and deformed vascular bed (52). The result is diminished respiratory volume and function. According to Behnke et al., ROS play a major role in lung toxicity and development of BPD (53). The defence system of hypoxia is already matured in utero by HIF-1 alpha (hypoxia-inducible factor). Triggered by low O2 inside the cell, it induces, among others, formation of new blood vessels (54). Hyperoxia in turn leads to destabilization of HIF, resulting in diminished vascularity and alveolarization (55). VEGF plays an

important role in lung development by inducing embryonic vasculogenesis, vasodilation via NO, differentiation of type 2 pneumocytes, and activation of immune cells (56). It was discovered that infants who died with BPD showed decreased levels of VEGF and VEGF receptor 1. Experimental research with rodents exposed to hyperoxia revealed a reduced concentration of VEGF in the lungs as well as impaired expression of VEGF receptors 1 and 2 (57). These changes are irreversible, potentially contributing to ongoing lung injury in infants with BPD. A study from Wang et al. correlates with these results (58). They exposed preterm rat neonates to O2 therapy with or without episodes of hyperoxia or hypoxia. Those rodents experiencing varying O2 levels had impaired lung development and antioxidative activity and disrupted HIF-1 alpha. Supplementing VEGF via gene therapy allows improved lung development, as shown in an experimental study (59).

In contrast, the antioxidant system remains immature until the 37th week of gestation, and the transition of maternal non-enzymatic antioxidants occurs just before birth (53). Detrimental effects of ROS include disturbance of cellular structures, especially mitochondria, causing enhanced ROS production and cell death. Damage to pulmonary endothelium and epithelium attracts inflammatory cells like leukocytes and neutrophils, further aggravating inflammatory injury, thereby impairing gas exchange.

The team of Lorente-Pozo focused on epigenetic changes induced by O2 therapy in preterm infants. According to their results, DNA and histone modification correlate with O2 saturation, influencing genes important for inflammation and renewal in the context of BPD (60). This could influence long-term consequences, according to Saugstad et al. (61). A newer study by Lorente-Pozo et al. focused on the effects of hyperoxia-induced epigenetic changes to neurodevelopment. 19 preterm infants received either more or less than 500 ml of O2 supplementation per kilogram of body weight. Among the study group with higher O2 administration, one gene showed hypermethylation at the two-year follow-up. It is associated with disturbed development of the nervous system and intellect, which was depicted by lower motor composite scores compared to the group with lower O2 (62). Measures to treat BPD by supplementing antioxidants have no therapeutic evidence so far. Oral vitamin A administration was investigated in a multicenter, double-blind, placebo-controlled trial with 915 infants with a mean gestational age of 26.5 weeks and a mean birth weight of 765 grams (63). The investigated outcome was a decrease in moderate or severe BPD or death in extremely low birth weight infants. Meyer et al. concluded vitamin A supplementation is safe but inefficient to decrease the incidence of defined outcomes. Caffeine is administered to preterm infants to stimulate the respiratory center and prevent apnea. Beneficial effects were also seen in relation to BPD by reducing the necessary time of positive pressure ventilation (64). An experimental study by Weichelt et al. tested whether hyperoxia-mediated pulmonary inflammation is preventable by caffeine

administration (65). O2 therapy in preterm infants causes the release of proinflammatory cytokines and leukocytes. Six-day-old rat pups with lung injury received either solely O2 therapy or additional caffeine. Effects were evaluated by chemokine, cytokine, and leukocyte detection. The results showed alveolar tissue destruction and upregulation of inflammatory response at hyperoxia as well as prevention thereof by antioxidant effects of caffeine administration. Inhaled nitric oxide (iNO) is used in term infants to cause vasodilation and bronchodilation via activation of cyclic guanosine monophosphate during respiratory failure. A review analysis of Barrington et al. failed to show benefit of iNO treatment for preterm infants with respiratory stress related to outcomes of death, BPD, or serious brain injury (66). The authors suspect that the cause lies in the difference between preterm and term infants regarding the pathology of respiratory failure as well as the effects of adverse events of iNO. A review of Obst et al. evaluates the effect of hyperoxia and consequential ROS formation on the lung-brain axis of preterm newborns (67). The high O2 tension causes defective development of lung and neuronal tissue, potentially leading to BPD and encephalopathy of prematurity (EOP). The latter is defined by myelination defects and white matter damage causing impaired neurodevelopment. The hypothesis of interrelation between damage of the brain and lungs by ROS is supported by experimental studies with rodents (68), (69). Administration of the antioxidant superoxide dismutase (SOD) after hyperoxic therapy protected pulmonary development in newborn mice and cognitive capacity in adult mice. According to Obst et al., hyperoxia related ROS production triggers the release of proinflammatory cytokines. Immune cells, alveolar macrophages in the lungs, and microglia in the brain get activated as illustrated in figure 15 (Obst et al., 2022, page 5).

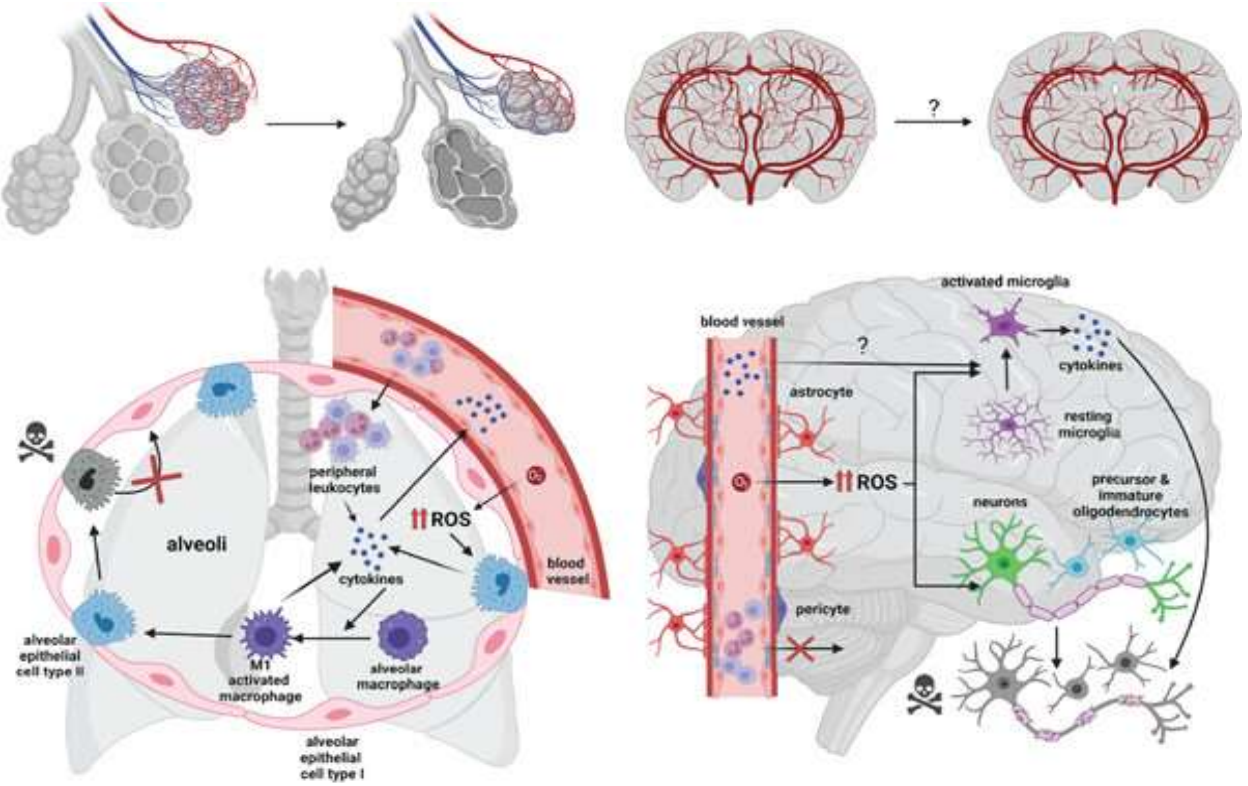


Figure 15. Hyperoxia-induced morphological changes and inflammatory responses in the developing brain and lung

This is supported by the studies of Felderhoff-Mueser et al. and Hirani et al., who showed that suppression of certain interleukins, which stimulate fever, inflammation, and tissue destruction, reduced hyperoxia-related damage to the brain and lung (70), (71). The difference between the two organs lies in the fact that hyperoxic lung injury is connected with invasion of peripheral leukocytes, while the BBB likely prohibits this (72). Hyperoxia disturbs the vascularization in lungs and cortical vessels in the brains of neonatal rats (73). Brain injury is restricted to certain areas like white matter and is defined by cellular death of premature oligodendrocytes leading to decreased myelination (67). This potentially leads to reduced neurocognitive function. Unlike in lungs, therapeutic approaches with iNO regarding brain injury revealed beneficial effects like amelioration of oligodendrocyte quantity and myelination in white matter (74). Therapy with supplementation of erythropoietin in rats exposed to hyperoxia seems to have advantageous effects on both lungs and brain, although dosing has to be further examined (75), (76), (77).

Another tissue that is highly susceptible to the postnatal high and fluctuating partial pressure of O2 is the immature retina. Especially prematurely born infants receiving O2 administration are at risk. Even though nowadays stricter rules are applied to neonatal O2 therapy, the incidence of retinopathy of prematurity (ROP) remains the same. One reason for this could be the higher survival rates of infants who are born extremely preterm and/ or with low birth weight. The pathophysiology of this vascular disease can be divided into two phases as depicted in figure 16 (Hellsröm et al., 2013, page 1446). During the first phase, hyperoxia ceases the action of VEGF and erythropoietin, leading to disturbed retinal vascularization. Since the retina is developing, the metabolic demand increases, leading to relative hypoxia. This triggers formation of new vasculature inside and outside the retina, encompassing phase two (78).

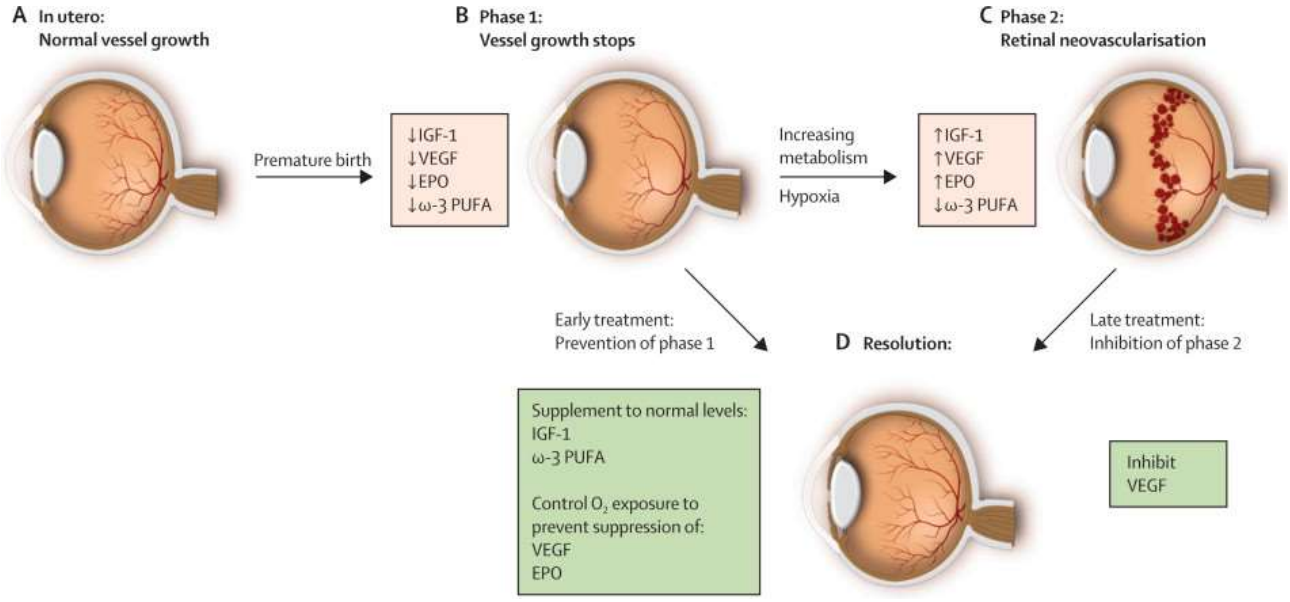


Figure 16. Progression of retinopathy of prematurity

The consequences are bleeding and formation of fibrovascular membranes, which can ultimately end in retinal detachment. Premature birth before the 28th week interrupts the maternal supply of insulin-like growth factor 1 (IGF-1), further inhibiting physiological development of cells, including those of neuronal and vascular tissue (79). The structure and function of the hypoxia-induced new retinal vessels are deficient, resulting in fibrosis and retinal separation. In most cases, the formation of defective vasculature is self-limiting. Neuronal deficits of photoreceptors can remain, regardless of the severity of ROP.

Clinical studies investigated factors promoting the transition from phase one to phase two (80), (81). The authors supposed extreme prematurity as a risk factor for ROP formation due to the fact that it appeared earlier in infants with a lower gestational age compared to more mature infants. A higher gestational age of more than 28 weeks could not prevent ROP formation in the case of 100% O2 administration, according to a study by Shah et al. (82). Observational studies claimed to show a reduction in the incidence of severe ROP as well as surgical treatment interventions for ROP patients by titrating postnatal O2 therapy to values <95% in extremely preterm or very low birth weight infants. The SUPPORT trial from Carlo et al. (83) intended to find confirmation thereof and provide a range of O2 saturation. A randomized controlled trial with 1316 preterm infants born before the 28th week of gestation either received O2 ranging from 85-89% or 91-95%. While the incidence of severe ROP was significantly lower in the study group, with lower O2 titration, the mortality was increased in this group which is visible in figure 17 (Carlo et al., 2010, page 12).

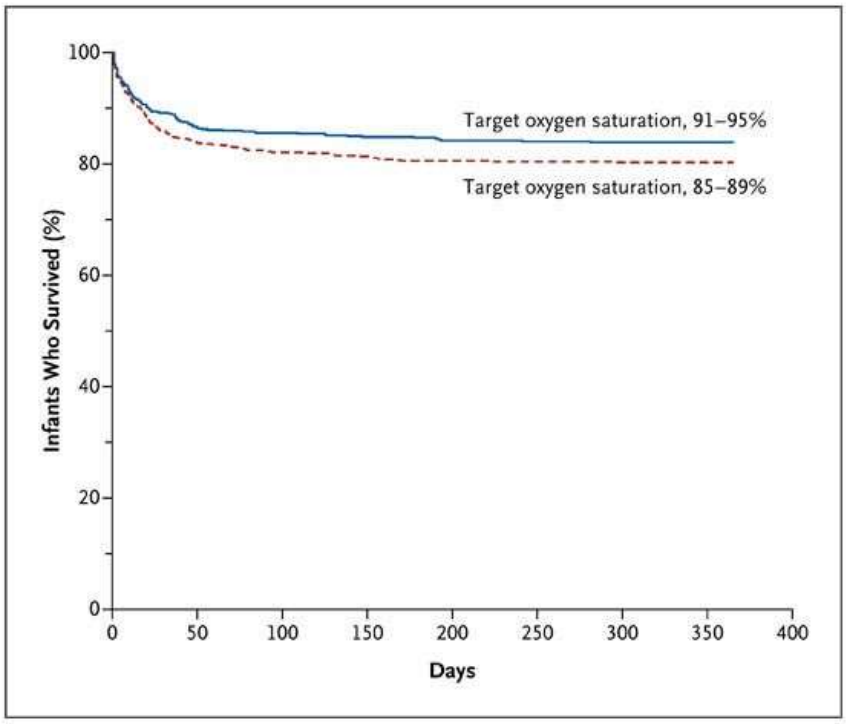


Figure 17. Kaplan–Meier Estimate of Survival to Hospital Discharge, Transfer, or 1 Year of Life

The authors call this discovery concerning since a tendency towards restricted O2 therapy for ROP prevention can be seen.

Two different classifications of retinopathy are defined. Figure 18 (Hellström et al., 2013, page 25) depicts the international classification of retinopathy of prematurity from 2005. Whether the pathology is classified as mild or severe depends on how far it extends across the retina, which is divided into three zones.

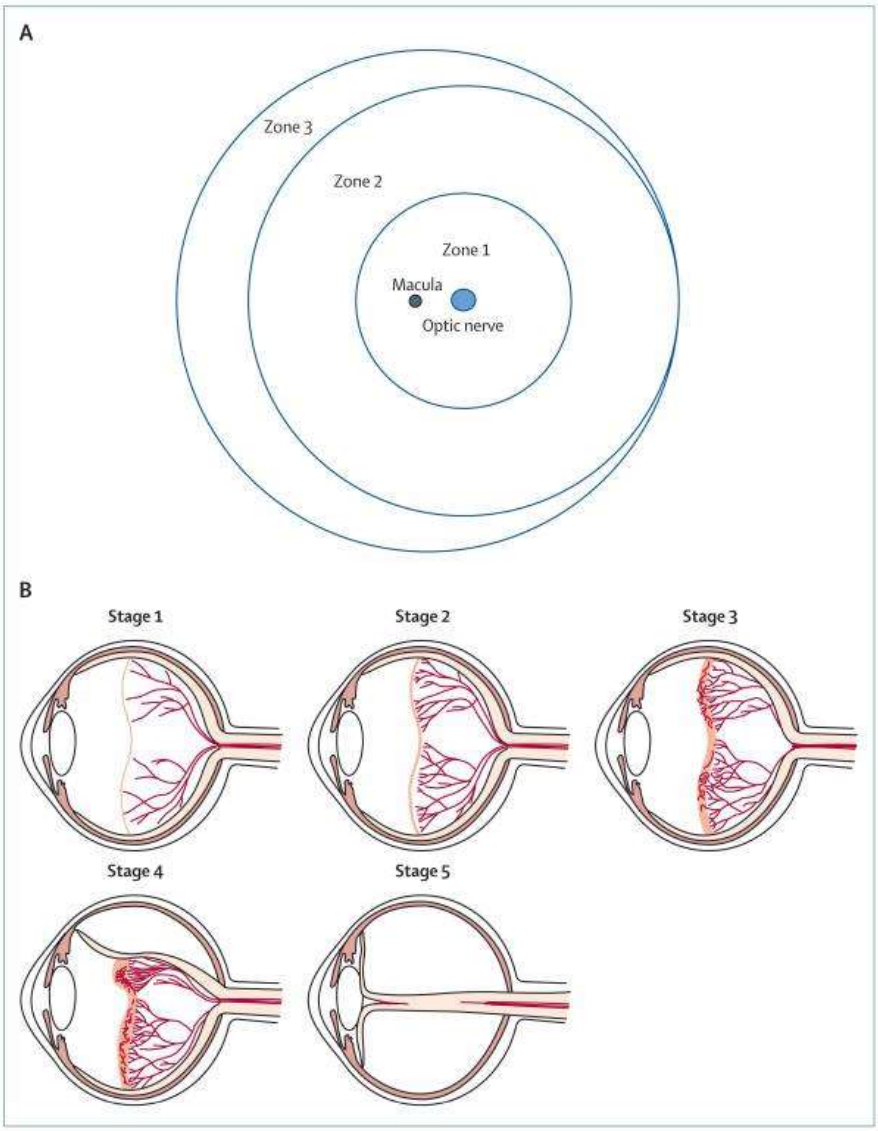


Figure 18. Zones and stages of retinopathy of prematurity

Stages 1 and 2 are mild, expressing a border between vascularized and non-vascularized parts of the retina. In most cases these stages are self-limiting. Stage 3 is characterized by fibrotization and neovascularization and represents the point at which either regression or aggravation takes place. Disease progression to stage 4 can be recognized by vascular dilation and torsion, also called plus disease. Blindness arises during stage 5 due to retinal detachment. The ETROP study redefined ROP according to treatment indication. Type 1 necessitates treatment; type 2 can be followed up (84).

A Swedish research team developed the WINROP algorithm to predict ROP development. Weekly measurements of neonatal body weight provide the possibility to predict those infants who will develop stage 3 ROP. It should be used in combination with other screening tools since the degree of sensitivity and positive predictive value vary in different studies (85), (86), (87). This screening tool allows a reduction in patients undergoing fundoscopy and timely treatment intervention if necessary (78). Moderate to late preterm infants cannot be assessed by WINROP. According to the ETROP study, treatment aims to reduce retinal destruction and prevent detachment in type 1 cases (88). Previously used cryotherapy got replaced by transpupillary laser coagulation treatment. According to ETROP (88) early intervention in high-risk ROP, like plus disease, improves both structural integrity and functional vision. Those patients with spontaneously regressing stages of ROP could not profit from the intervention. Yang et al. investigated the long-term effects of ROP and laser treatment in children aged 7 years. Although the overall visual outcome was favorable, complications like strabismus, anisometropia, and myopia were detected in patients who received laser treatment (89). The authors suggest close follow-up for treatment possibilities.

10 CONCLUSION

Oxygen therapy remains an essential component of treatment in many critical clinical situations. The aim of this master's thesis was to analyze the outcome of oxygen administration and determine whether different clinical settings pose different demands on oxygen therapy. A major challenge in oxygen therapy is the lack of large-scale, high-quality studies defining the optimal oxygenation targets for critically ill patients. Existing evidence shows that both hypoxia resulting in disturbance of cellular energy production and hyperoxia with reactive oxygen species causing inflammation and decreased perfusion can have deleterious effects on patients.

During the return of spontaneous circulation following a cardiac arrest the partial pressure of oxygen should be titrated to values of 60 to 105 mmHg (90).

In view of the paucity of high-certainty evidence to define optimal oxygenation targets for patients with sepsis and septic shock, the most prudent approach appears to be to aim for a moderate partial pressure of oxygen between 75 and 105 mmHg during intensive care (91).

With regard to cardiac surgery, the American heart association advocates the maintenance of partial pressure of oxygen within the range of 80 to 110 mmHg (92).

In neonatal care the American heart association (44) and European Resuscitation Council (45) recommend for the adaption of oxygen administration according to the gestational age. Resuscitation of moderate to late preterm infants should be initiated with 21 to 30% oxygen. Term born babies

appear to benefit from receiving oxygen at a concentration of 21% shortly after birth. Data for moderate to extremely preterm babies are inconsistent thus therapy should be adapted individually.

Summarizing the results of this review, it can be inferred that there are no exact guidelines for optimal clinical oxygen therapy. In general, providing oxygen supplementation within a moderate range, keeping saturation level up to 97%, appears to be sufficient. Given today's knowledge, each administration should be adjusted to the specific situation and patient. Therefore, further high-quality clinical studies are urgently needed in order to formulate precise evidence-based recommendations on oxygen therapy.

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