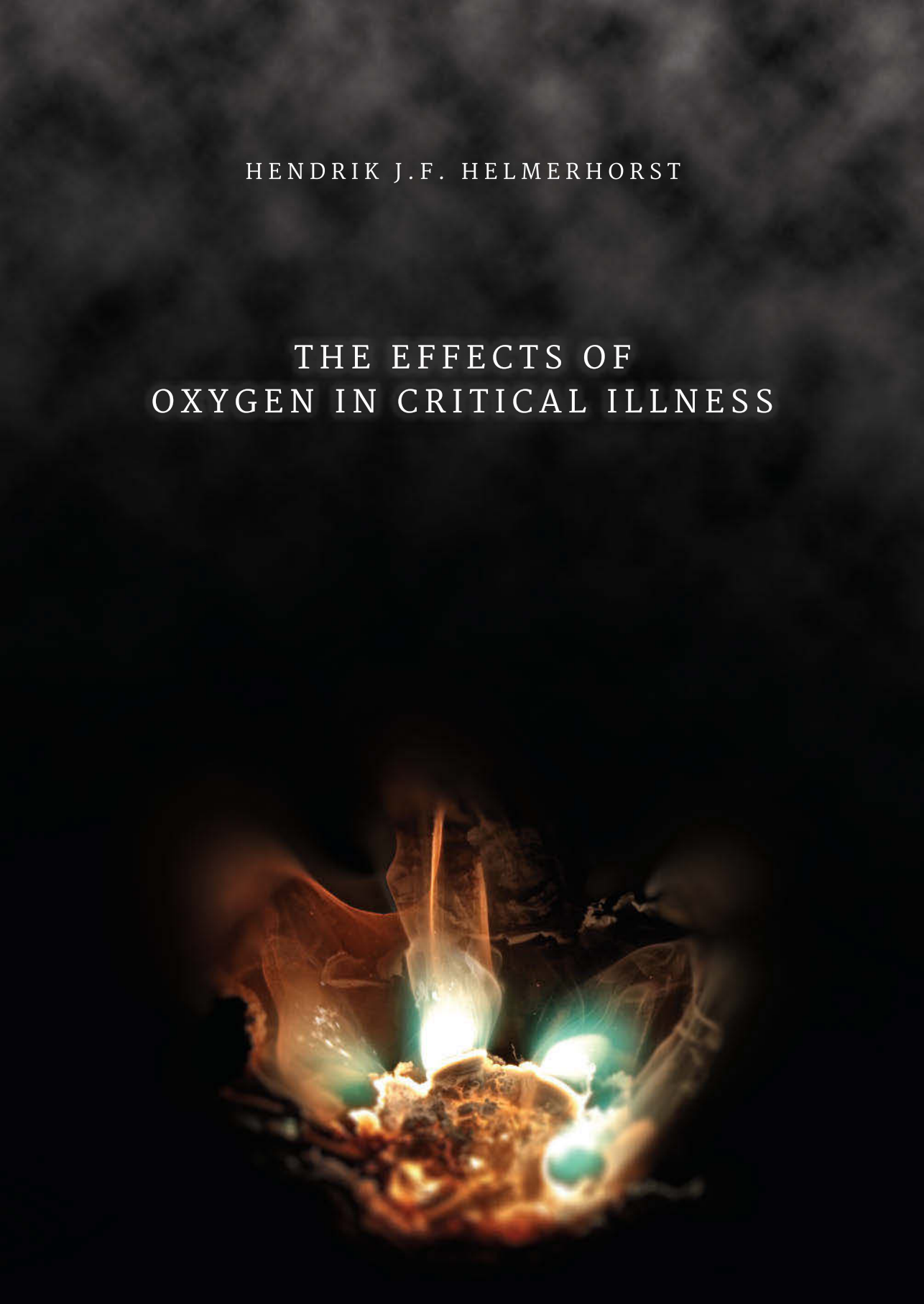
HENDRIK J.F. HELMERHORST

THE EFFECTS OF OXYGEN IN CRITICAL ILLNESS



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Hendrik J.F. Helmerhorst

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THE EFFECTS OF OXYGEN IN CRITICAL ILLNESS

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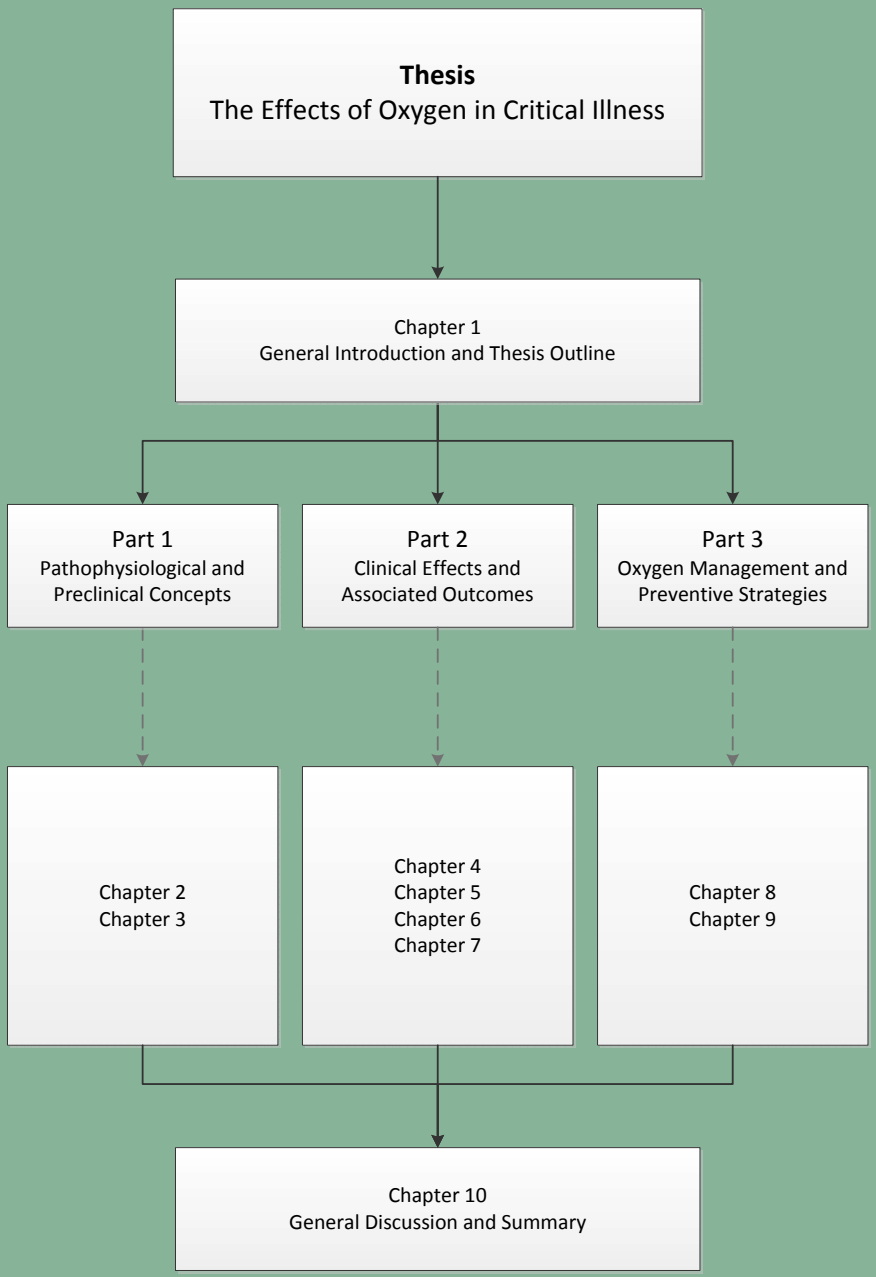
1

GENERAL INTRODUCTION

ABSTRACT

In this thesis we explore the pathophysiological and preclinical concepts underlying the effects of supraphysiological oxygenation (part 1), assess the clinical effects of hyperoxia in critical care (part 2) and investigate preventive strategies in oxygen management by promoting conservative oxygenation in the intensive care unit (part 3).



SUBJECT AND SUSPECT: OXYGEN

Owing to its indispensable nature, oxygen may the most appealing element in life and among the most important components for therapy in critical care. It is the basis for aerobic cell metabolism and a prerequisite for life by fueling the mitochondria and supplying energy to the body. Supplemental oxygen is routinely administered in emergency situations and has life-saving potential in critically ill patients. Therefore it is a cornerstone in the treatment of patients in the intensive care unit. However, Swiss-born Renaissance physician and father of toxicology, Paracelcus noted: "Alle Dinge sind Gift, und nichts ist ohne Gift. Allein die Dosis macht, daß ein Ding kein Gift ist". In free interpretation: the dose makes the poison. This accounts for many aspects in medicine, but it may also be well applicable to the essential oxygen molecule. Following the independent discovery of oxygen by the chemists Scheele, Priestley and Lavoisier between 1772 and 1775, Joseph Priestley was the first to suggest that dephlogisticated air (oxygen) may also have adverse effects.

As a deficiency in the amount of oxygen in the tissues (hypoxia) is a feared complication for all patients, oxygen therapy is universally applied when impaired oxygen delivery to vital organs is suspected or anticipated. Under these circumstances, hypoxia is aggressively prevented by clinicians, but oxygen may also exert harmful effects, when it is administered in supraphysiological doses (hyperoxia).

Hyperoxia can be defined as a state where oxygen administration exceeds the concentrations in ambient air (21%) or where the achieved oxygen levels of arterial blood are higher than in spontaneously breathing healthy subjects at sea level (supraphysiological). In order to prevent or counteract hazardous hypoxic episodes, oxygen is usually administered using nasal cannulas, face masks or mechanical ventilators under the paradigm "the more, the merrier". The effects of supplemental oxygen are monitored by measuring the oxygen saturation in circulating red blood cells using red and infrared light (pulse oximetry). In general, this is a very useful method to roughly estimate the current oxygenation status of the patient, but its interpretation is limited in several situations and clinicians do not fully rely on this measurement. Importantly, pulse oximetry is characterized by a ceiling effect in which complete saturation (100%) of the oxygen carrying molecule (hemoglobin) is indicated but a further increase in the partial pressure of oxygen in the arterial blood (PaO_2) is still possible. In addition, saturation levels below 70% are determined by extrapolation as pulse oximeters are not calibrated for extremely low saturations. Actual oxygenation is therefore more accurately assessed by arterial blood gas (ABG) measurements for which intermittent sampling and analysis by clinical laboratories or point-of-care devices is required. Such repeated measurements are time consuming, whereas pulse oximetry is a non-invasive method allowing for continuous monitoring at the bedside. Both techniques are used concurrently in the intensive care unit (ICU) in order to provide a continuous estimation of the arterial oxygenation. When supranormal oxygen levels are achieved, the pulse oximeter usually indicates 100% oxyhemoglobin saturation, but the severity and exact degree of hyperoxia can only be assessed with delay by determining the actual partial pressure of arterial oxygen using ABG analysis. Hence, because an excess of oxygen is difficult to monitor on a continuous basis and oxygen is generally administered in a liberal manner, arterial hyperoxia is frequently encountered in the intensive care unit (ICU) (1-3).

FRIEND AND FOE

A high fraction of inspired oxygen (FiO_2) is highly effective in promoting the oxygen content of arterial blood during specific emergency settings. In case of injured lungs or when the oxygen uptake or carrying capacity is impaired, high FiO_2 levels may be necessary to preserve adequate oxygenation. However, hyperoxia may contribute to pulmonary inflammation, edema and tissue injury (biotrauma) in concurrence with the potential side effects of positive airway pressures (barotrauma) and volumes (volutrauma) applied by mechanical ventilation, also known as ventilator-induced lung injury (4, 5). When the lungs are relatively healthy, supplemental oxygen typically leads to increased and supranormal PaO_2 levels. Arterial hyperoxia induces vasoconstriction in most vascular beds which can be beneficial during vasodilatory shock but may also impose risk when organ perfusion is impaired. Furthermore, arterial hyperoxia has been associated with poor clinical outcomes in several cohort studies. A causal relationship has been questioned, but hyperoxia does have a strong potential to induce hemodynamic changes, lung injury and oxygen toxicity (6-12). Oxygen toxicity by free radicals is a well-established condition since the pioneering efforts of Lorrain Smith and Paul Bert in its discovery in the late 19th century (13). The description historically includes deleterious effects on the central nervous system and pulmonary intoxication. Oxygen free radicals are commonly referred to as reactive oxygen species (ROS) and are versatile molecules with an important role in cell signaling and homeostasis. ROS are formed during aerobic metabolism but physiological levels may be exceeded during environmental stress or when supplemental oxygen is administered. Critical illness may be viewed as an important environmental stressor and a typical setting for inadequate levels of ROS. When antioxidant systems are insufficient, supplemental oxygen can cause accumulation of oxygen radicals and may initiate or perpetuate oxygen toxicity. These potential side-effects of supplemental oxygen are pertinent to divers (14), pilots and premature infants (15, 16) but are of special concern in mechanically ventilated and oxygen supported critically ill patients (17).

TRIAL AND ERROR

The effects of oxygen have been comprehensively studied in experimental animal models but data from clinical trials in the intensive care unit are scarce. Compelling evidence on the time- and dose-response relationship between arterial hyperoxia, physiological parameters and clinical outcomes of critically ill subgroups is lacking. Strikingly, oxygenation guidelines are available for only a limited number of subgroups, and these are not easily extrapolated to universal recommendations. This may lead to a suboptimal treatment policy in the intensive care unit as long as safe target ranges are not exactly known. Consequently, clinicians find themselves in a quandary during oxygen therapy when pursuing physiological PaO_2 ranges and achieve adequate oxygenation in their patients.

EVIDENCE AND SETTLEMENT

In this thesis, we aimed to expand on the available evidence and fill in crucial knowledge gaps regarding oxygen therapy in the intensive care unit.

Considering the beneficial but also harmful effects, oxygen can be regarded as a molecule yielding two competing harms, as a double-edged sword, a Janus face, and a representation of Dr. Jekyll and Mr. Hyde. Therefore, an essential research question regarding oxygen therapy emerges: the more oxygen the better or can there be too much of a good thing and may less be more?

In this matter, conservative oxygen therapy has been proposed as a therapeutic strategy in which both hypoxia and hyperoxia are actively and concomitantly prevented. In contrast to liberal oxygen administration the rationale is to prevent harm by iatrogenic hyperoxia, while preserving adequate tissue oxygenation. However, the feasibility and effectiveness of such strategies have not been studied and the effects on clinical outcomes remain to be determined.

Hence, the aims of this thesis were to

1. assess preclinical effects and summarize the pathophysiological characteristics of hyperoxia;
2. review previous clinical findings and evaluate the epidemiology of hyperoxia in critical care;
3. assess the time- and dose-response effects in specific ICU populations and explore preventive therapeutic strategies.

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OUTLINE OF THE THESIS

The general purpose of this thesis is to investigate the pathophysiology and epidemiology of hyperoxia in critical illness and explore strategies for prevention of oxygen toxicity in the intensive care unit.

- In **Chapter 2**, we give an introduction to the pathophysiological concepts of oxygen toxicity and review the literature for recent experimental, translational and clinical data, and further discuss the implications for therapy.
- In **Chapter 3,** we investigate the time- and dose response effects of supplemental oxygen in an experimental mouse model using hyperoxic mechanical ventilation.
- In **Chapter 4**, we explore the acute hemodynamic and microcirculatory changes during increased oxygen supply in mechanically ventilated patients in the intensive care unit after coronary artery bypass grafting surgery
- In **Chapter 5**, we describe the independent and combined effects of the partial pressures of both arterial carbon dioxide and arterial oxygen in a multicenter cohort of patients admitted to Dutch intensive care units after cardiac arrest.
- In **Chapter 6**, we systematically review the literature for cohort studies comparing arterial hyperoxia to normoxia in critically ill adults and performed a meta-analysis and meta-regression of the results.
- In **Chapter 7**, we evaluate previously used and newly constructed metrics of arterial hyperoxia and systematically assess their association with clinical outcomes in different subgroups in the intensive care unit.
- In **Chapter 8**, we identify the common beliefs and self-reported attitudes of critical care physicians and nurses on oxygenation targets and compared this with actual treatment of patients in three tertiary care intensive care units in the Netherlands.
- In **Chapter 9,** we study the feasibility, effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the same three intensive care units.
- In **Chapter 10,** we discuss the benefits and possible harms of oxygen therapy during critical illness, review the current evidence and summarize the findings of the present thesis.

Part I

PATHOPHYSIOLOGICAL AND PRECLINICAL CONCEPTS

2

BENCH-TO-BEDSIDE REVIEW: THE EFFECTS OF HYPEROXIA DURING CRITICAL ILLNESS

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ABSTRACT

Oxygen administration is uniformly used in emergency and intensive care medicine and has life-saving potential in critical conditions. However, excessive oxygenation also has deleterious properties in various pathophysiological processes and consequently both clinical and translational studies investigating hyperoxia during critical illness have gained increasing interest. Reactive oxygen species (ROS) are notorious by-products of hyperoxia and play a pivotal role in cell signaling pathways. The effects are diverse but when the homeostatic balance is disturbed, ROS typically conserve a vicious cycle of tissue injury, characterized by cell damage, cell death and inflammation. The most prominent symptoms in the abundantly exposed lungs include tracheobronchitis, pulmonary edema, and respiratory failure. In addition, absorption atelectasis results as a physiological phenomenon with increasing levels of inspiratory oxygen. Hyperoxia-induced vasoconstriction can be beneficial during vasodilatory shock but hemodynamic changes may also impose risk when organ perfusion is impaired. In this context, oxygen may be recognized as a multifaceted agent, a modifiable risk factor and a feasible target for intervention. Although most clinical outcomes are still under extensive investigation, careful titration of oxygen supply is warranted in order to secure adequate tissue oxygenation while preventing hyperoxic harm.

INTRODUCTION

Oxygen is a vital element in human survival and plays a major role in a diverse range of biological and physiological processes. In medical practice, it is among the most universally used agents for the treatment of critically ill patients (1) and part of the routine treatment in acute shock and emergency medicine (2). In order to ensure sufficient oxygenation, oxygen therapy during mechanical ventilation, anesthesia and resuscitation usually exceeds physiological levels. However, Renaissance physician Paracelsus noted: "nothing is without poison – the poison is in the dose". This accounts for many aspects in medicine, but it may also be well applicable to the oxygen molecule (3). The concept of oxygen toxicity has been described in the late 19th century following the pioneering efforts of Lorrain Smith and Paul Bert, but it was not until a century later that the effects of hyperoxia were increasingly studied. Although several lines of evidence indicate that hyperoxia may be harmful, robust interventional studies are still limited. In order to develop adequate recommendations for optimal oxygen levels it is important to extend our current understandings of hyperoxia-induced injury. The aim of this review is to provide a comprehensive overview of the effects of hyperoxia from the bench and the bedside. The first part will focus on established insights and recent experimental and translational advances; the latter part addresses pathophysiological concepts, clinical studies and implications for therapy.

Pathogenesis from the benchside

Reactive oxygen species

Reactive oxygen species (ROS) are versatile molecules that can be essential in the regulation of intracellular signaling pathways and in host defense (4). However, ROS have also repeatedly been postulated to be of major significance in tissue damage, organ dysfunction and clinical disease. When referring to oxygen toxicity, it is frequently assumed that it is not oxygen itself that exerts toxic effects but merely the ROS that are generated as an undesirable byproduct of adenosine triphosphate synthesis during aerobic cellular metabolism. The implications for the lungs are probably the most prominent as lung tissue is continuously and abundantly exposed to oxygen and its byproducts. In physiological circumstances, ROS are formed in the electron transport chain during proton transport across the inner mitochondrial membrane. Mitochondrial oxidative phosphorylation is the most important source of oxygen species, but ROS may also be generated in response to exogenous stimuli, such as microbes, cytokines and xenobiotics (5). Antioxidant tasks are accomplished by enzymes as catalases, glutathione peroxidases, thioredoxins and peroxyredoxins. These enzymes use electron donors in order to avoid the intermediate formation of the hydroxyl radical (OH·), which is a strongly reactive oxidant. In this process superoxide dismutase (SOD) is an important antioxidant enzyme as it efficiently reduces the concentration of the superoxide anion ($O_2^{\cdot -}$), by facilitating its rapid conversion in hydrogen peroxide (H_2O_2) or oxygen (O_2). In general, ROS generation from mitochondria increases with oxygen tension and is dependent on the clinical balance between the underlying condition and oxygen supply (6). In response to bacterial invasion neutrophils can also produce large amounts of ROS that may initially be beneficial in the host defense against several pathogens. Fortunately, the lungs are

principally well protected against oxygen toxicity by adequate intra- and extracellular antioxidant activity. Beside this physiological activity, additional antioxidants can be recruited in the epithelial lining fluid (7). However, when the production of ROS exceeds the limits of counteraction by antioxidant responses, ROS concentrations reach inadequate levels and a cellular state of oxidative stress manifests. Oxidative stress refers to the imbalance caused by increased ROS formation or deficient oxidant suppressors (8). When antioxidant systems are insufficient during critical illness and mechanical ventilation, supplemental oxygen can cause accumulation of oxygen radicals and may initiate or perpetuate oxygen toxicity. Moreover, ROS control can be markedly influenced by ageing, genetic factors and pharmacochemical agents (6).

Cell death

When the delicate homeostatic balance is disturbed, oxidative stress leads to damage of nucleic acids, proteins and lipids, resulting in cell death by both apoptotic and necrotic pathways (9). Necrosis is characterized by incomplete apoptosis and supported by integrity loss of the cell membrane and cytoplasmic swelling. Programmed cell death by apoptosis can be achieved through extrinsic or intrinsic pathways, concomitantly. The *extrinsic* pathway is triggered by extracellular signals that stimulate intracellular apoptotic cascades after binding the cell membrane. The *intrinsic* apoptotic pathway is initiated by increased mitochondrial ROS formation. Subsequently, the opening of transition pores is facilitated making the outer mitochondrial membrane more permeable for pro-apoptotic components. These components can then pass to the cytoplasm and induce a state of intracellular stress. When this occurs in both endothelial and epithelial cells, lytic damage and cell death contribute to interstitial pulmonary edema and impaired gas exchange by means of alveolar collapse and disintegration of the alveolar-capillary barrier.

Cell damage and inflammatory pathways

In addition to direct cell death by necrosis or apoptosis, cellular disruption caused by hyperoxia and ROS has been shown to release endogenous damage-associated molecular pattern molecules (DAMPs) that alert the innate immune system (10-12). DAMPs, or alarmins, are cell fragments released during cellular dysfunction and sterile injury and act as pleiotropic modulators of inflammation. During oxidative stress, mitochondrial damage is a pivotal cause of extracellular hazardous content including both free radicals and DAMPs. As they resemble bacterial DNA, circulating mitochondrial DAMPs are efficiently recognized by pattern recognition receptors and activate polymorphonuclear neutrophils (PMNs). Subsequently, PMNs release interleukins and contribute to a sterile inflammatory reaction and, ultimately, neutrophil-mediated organ injury. In response to hyperoxia-mediated ROS production, resident lung cells initiate the release of various cytokines. Chemotactic factors orchestrate the inflammatory response by attracting inflammatory cells to the pulmonary compartment. Recruited neutrophils and monocytes are in turn significant sources of additional ROS, conserving a vicious cycle leading to further tissue damage (Fig. 1).

Under enduring conditions of injury to pulmonary epithelium and increasing alveolar permeability, cytokines can translocate from the alveolar space to the systemic circulation, creating

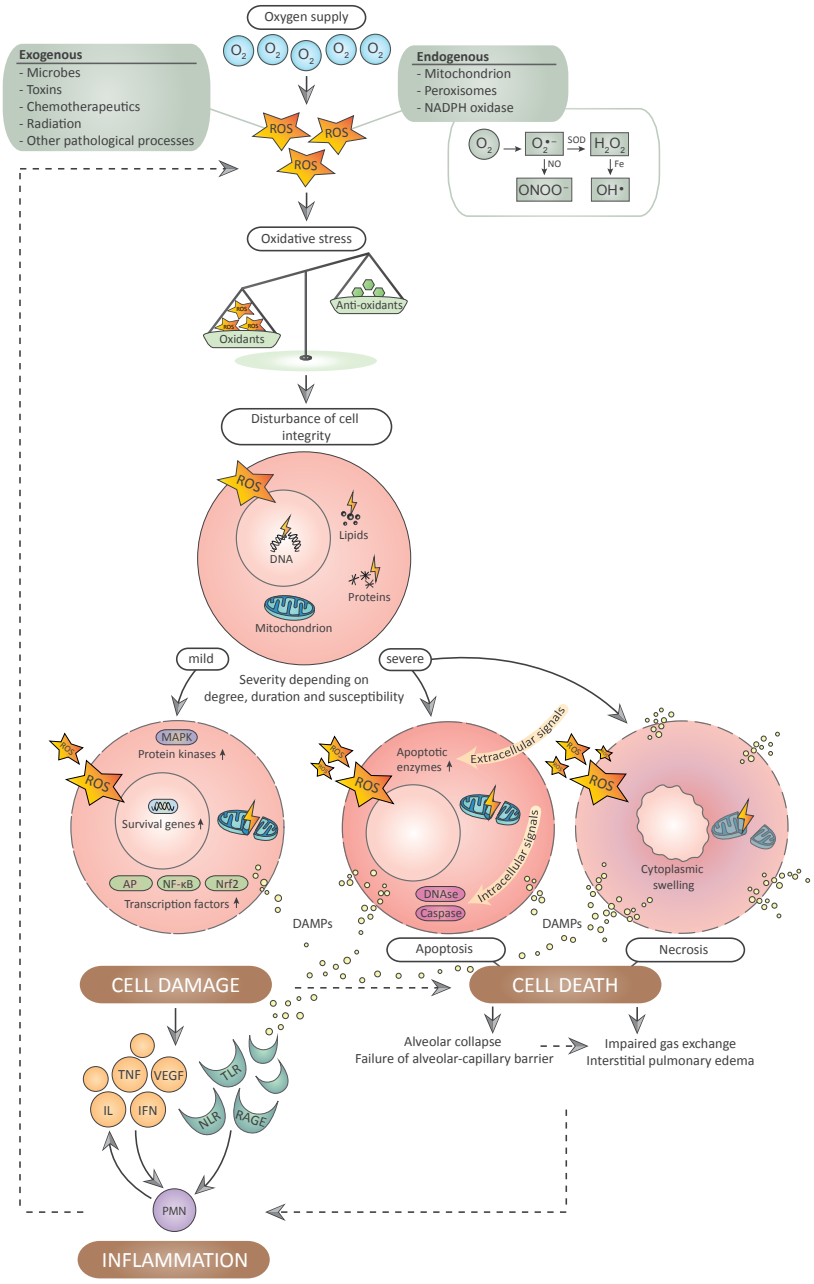

Figure 1. Vicious cycle of hyperoxia induced cell injury.
AP, activator protein; DAMP, damage-associated molecular pattern molecules; H_2O_2, hydrogen peroxide; IFN, interferon gamma; IL, interleukin; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NLR, nodlike receptor; Nrf2, nuclear factor-2 erythroid related factor-2; O_2, oxygen; O_2 ·−, superoxide; OH·, hydroxyl radical; ONOO−, peroxynitrite; PMN, polymorphonuclear neutrophil; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

a systemic inflammatory response, in which cytokines are efficiently activated and phagocytosis by alveolar macrophages is hampered (13). Cytokine concentrations decrease after long-term exposure, suggesting that a fast upregulation of inflammatory action is followed by a gradual impairment of the innate immune system (14). Besides mitochondrial damage, the inflammatory actions of oxygen are importantly modulated by the hypoxia-inducible transcription factor (HIF) (15, 16). HIF-1αis thought to be upregulated during relative changes in oxygenation and accordingly responds to normoxia as a relative hypoxic state directly after hyperoxia. Through this mechanism, intermittent hyperoxia may trigger a paradoxical phenomenon in which the genetic expression of inflammatory mediators and erythropoietin (EPO) is stimulated in the absence of true tissue hypoxia (17).

Animal studies

Principal insights in hyperoxia-induced mechanisms have been obtained from experimental models. The first animal studies documented structural morphologic and biochemical changes in the lungs of a wide variety of animal species that were exposed to hyperoxia (18). Pioneering studies using conscious dogs postulated that normobaric hyperoxia decreased metabolic rate and altered hemodynamics (19, 20). These findings were subsequently reproduced in primates in whom progressive pulmonary injury, interstitial edema and inflammatory activation were observed (21). In later experiments, biochemical effects of ROS and interventional targets on the molecular level were more intensively studied in spontaneously breathing animals in hyperoxic environments and showed both detrimental and protective potential (22-26). Recent experiments were performed in mechanically ventilated rodents, rabbits and pigs mimicking the clinical environment of critically ill patients (27-31). In this context, the interaction between injurious ventilation and concurrent hyperoxia was shown to transcend lung injury by alveolar distention alone (22, 32-35). However, studies in mechanically ventilated animals are usually restricted to short exposure periods (32, 34-38), even though hyperoxia may induce time-dependent inflammation (23). In order to improve our understanding of the impact of long-term exposure to both mechanical ventilation and hyperoxia, future studies involving mechanical ventilation of longer duration and with clinically relevant settings are essential for a robust representation of the ICU environment.

Pathogenesis from the bedside

Hyperoxia induced tissue injury

Under normobaric circumstances, the side-effects of oxygen are initially restricted to the lungs. However, when hyperoxia manifests for prolonged periods or under hyperbaric conditions, other organs are concurrently at risk as more oxygen is dissolved in plasma (6). The amount of dissolved oxygen will readily increase at partial pressures of arterial oxygen (PaO_2) exceeding 100 mmHg. Oxyhemoglobin saturation is nearly complete when PaO_2 approaches this level and the carrying capacity of hemoglobin is therefore quickly overcharged with increasing fractions of inspired oxygen (FiO_2).

The harmful effects depend on underlying conditions, duration and degree of the hyperoxic exposure. Rigid thresholds where harm exceeds the perceived benefits are not exactly known and

may vary between subgroups (39). Most pathophysiological changes originate rapidly and are rather universal effects, but the effects of hyperoxia are assumed to be time- and dose-dependent (40). In general, excessive oxygen supply causes absorption atelectasis by displacement of alveolar nitrogen. The progressive washout of nitrogen coincides with the abundant presence of oxygen in the alveoli which, driven by a steep pressure gradient, rapidly diffuses into the mixed venous blood. As a result, the alveolar volume is markedly reduced and leads to increased ventilation/perfusion mismatch by (partial) alveolar collapse and impaired gas exchange, which can be attenuated by applying positive end-expiratory pressure (PEEP) (41). Impaired mucociliary clearance by hyperoxia further contributes to obstructive atelectasis and altered surfactant metabolism facilitates adhesive atelectasis through alveolar instability and collapse. Several lines of evidence indicate further effects of breathing high oxygen levels in animals and healthy subjects (1, 42), but evidence of pulmonary toxicity in a clinical scenario is limited (43). The pathological features of this condition are commonly referred to as the Lorrain Smith effect (44) and are characterized by tracheobronchitis, which can be accompanied by pleuritic pain, bronchial irritation, cough and sore throat. Symptoms may spread from the upper airways into the lungs where diffuse alveolar damage manifests and contributes to edema, vascular leakage, arteriolar thickening, pulmonary fibrosis and emphysema, reflected by progressive paradoxical hypoxia, dyspnea and tachypnea. Additionally, prolonged hyperoxic exposure alters the microbial flora in the upper airways and further increases the risk of secondary infections and lethality. Notably, these pulmonary effects are often in addition to the primary (e.g. pneumonia) and secondary lung injury (e.g. ventilator-induced lung injury), which are accompanied by inflammatory responses.

The central nervous system is typically the first to reveal symptoms from excessive ROS formation. The spectrum of neurological symptoms is referred to as the Paul Bert effect and ranges from nausea, dizziness and headache to vision disturbances (retinal damage), neuropathies, paralysis and convulsions (1).

Vascular effects of hyperoxia have been well documented and may have both harmful and beneficial effects. Arterial hyperoxia increases the systemic vascular resistance and induces vasoconstriction, which may impair organ perfusion, especially in the cerebral and coronary region (45-47). Accompanying cardiovascular alterations result from even short term exposure and include a decrease in heart rate, stroke volume and cardiac output (48). However, hyperoxia is not a universal vasoconstrictor in all vascular regions and blood flow may be redistributed to the hepatosplanchnic circulation in septic shock (1, 49). Alternatively, the administration of oxygen promotes hemodynamic stabilization during vasodilatory shock, decreases intracranial pressure by cerebral vasoconstriction and preserves tissue oxygenation during hemodilution (2, 50).

Clinical studies

Critical care

Recent studies assessing the clinical effects of arterial hyperoxia or normobaric supplemental oxygen in critical care are listed in Table 1.

Table 1. Studies assessing the clinical effects of arterial hyperoxia or supplemental oxygen in subgroups of critically ill patients

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Eastwood 2012 (51)	ANZ	Cohort	2000-2009	MV	152680	-	Hypoxia in first 24h of admission was associated with increased in-hospital mortality, but hyperoxia was not.
de Jonge 2008 (52)	NET	Cohort	1999-2006	MV	36307	+	High FiO_2, and both low PaO_2 and high PaO_2 in first 24h of admission were associated with in-hospital mortality
Suzuki 2014 (53)	AUS	Before-after pilot	2012	MV	105	+/-	Conservative oxygen therapy in mechanically ventilated ICU patients was feasible and free of adverse biochemical, physiological, or clinical outcomes while allowing a marked decrease in excess oxygen exposure
Aboab 2006 (41)	FRA	Experimental	NA	ARDS	14	+/-	In mechanically ventilated patients with ARDS the breathing of pure oxygen leads to alveolar derecruitment, which is prevented by high PEEP.
Austin 2010 (54)	AUS	RCT	2006-2007	COPD	405	+	Titrated oxygen treatment significantly reduced mortality, hypercapnia, and respiratory acidosis compared with high flow oxygen in acute exacerbations of COPD
Cameron 2012 (55)	NZL	Cohort	2005-2008	COPD	180	+	Serious adverse clinical outcomes are associated with both hypoxaemia and hyperoxaemia during acute exacerbations
Perrin 2011 (56)	NZL	RCT	2007-2009	Asthma	106	+	High concentration oxygen therapy causes a clinically significant increase in transcutaneous CO_2 during severe exacerbations
Bellomo 2011 (57)	ANZ	Cohort	2000-2009	CA	12108	-	Hyperoxia did not have a robust or consistently reproducible association with mortality
Elmer 2014 (58)	USA	Cohort	2008-2010	CA	184	+	Severe hyperoxia was independently associated with decreased survival to hospital discharge
Ihle 2013 (59)	AUS	Cohort	2007-2011	CA	584	-	Hyperoxia within the first 24h was not associated with increased hospital mortality
Janz 2012 (60)	USA	Cohort	2007-2012	CA	170	+	Higher levels of the maximum measured PaO_2 were associated with increased in-hospital mortality and poor neurological status on hospital discharge
Kilgannon 2010 (61)	USA	Cohort	2001-2005	CA	6326	+	Arterial hyperoxia was independently associated with increased in-hospital mortality compared with either hypoxia or normoxia

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Kilgannon 2011 (62)	USA	Cohort substudy	2001-2005	CA	4459	+	Supranormal oxygen tension was dose-dependently associated with the risk of in-hospital death
Kuisma 2006 (63)	FIN	RCT pilot	NA	CA	28	-	No indication that 30% oxygen with SpO_2 monitoring did worse than the group receiving 100% oxygen.
Lee 2014 (64)	KOR	Cohort	2008-2012	CA	213	-	Mean PaO_2 was not independently associated with in-hospital mortality
Nelskylä 2013 (65)	AUS	Cohort	2008-2010	CA	122	-	No statistically significant differences in numbers of patients discharged from the hospital and thirty day survival between patients with hyperoxia exposure and no exposure
Spindelboeck 2013 (66)	AUT	Cohort	2003-2010	CA	145	-	Increasing PaO_2 was associated with a significantly increased rate of hospital admission and not with harmful effects
Vaahersalo 2014 (67)	FIN	Cohort	2010-2011	CA	409	-	Hypercapnia was associated with good 12-month outcome, but harm from hyperoxia exposure was not verified
Miñana 2011 (68)	ESP	Cohort	2003-2009	ADHF	588	-	Admission PaO_2 was not associated with all-cause long-term mortality
Ranchord 2012 (69)	NZL	RCT pilot	2007-2009	STEMI	136	-	No evidence of benefit or harm from high-concentration compared with titrated oxygen
Stub 2012 (70)	AUS	RCT	2011-2014	STEMI	441	+	Supplemental oxygen therapy in patients with STEMI but without hypoxia increased myocardial injury, recurrent myocardial infarction, cardiac arrhythmia, and was associated with larger myocardial infarct size at six months. Further results anticipated.
Sutton 2014 (71)	ANZ	Cohort	2003-2012	Post cardiac surgery	83060	-	No association between mortality and hyperoxia in the first 24 h in ICU after cardiac surgery
Ukholkina 2005 (72)	RUS	RCT	NA	AMI	137	-	Inhalation of 30-40% oxygen within 30 min prior to endovascular myocardial reperfusion and within 4h thereafter reduced the area of necrosis and peri-infarction area, improved central hemodynamics, and decreased the rate of postoperative rhythm disorders as compared with patients breathing ambient air

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Zughaft 2013 (73)	SWE	RCT	NA	ACS	300	-	The use of oxygen during PCI did not demonstrate any analgesic effect and no difference in myocardial injury measured with troponin- t or in the morphine dose
Asher 2013 (74)	USA	Cohort	NA	TBI	193	-	PaO_2 threshold between 250 and 486 mmHg during the first 72 h after injury was associated with improved all-cause survival, independent of hypocarbia or hypercarbia
Brenner 2012 (75)	USA	Cohort	2002-2007	TBI	1547	+	Hyperoxia within the first 24h of hospitalization was associated with worse short-term functional outcomes and higher mortality
Davis 2009 (76)	USA	Cohort	1987-2003	TBI	3420	+	Both hypoxemia and extreme hyperoxemia were associated with increased mortality and a decrease in good outcomes
Quintard 2014 (77)	SUI	Cohort	2009-2013	TBI	36	+	Incremental normobaric FiO_2 levels were associated with increased cerebral excitotoxicity, independent from brain tissue oxygen and other important cerebral and systemic determinants
Raj 2013 (78)	FIN	Cohort	2003-2012	TBI	1116	-	Hyperoxemia in the first 24h of admission was not predictive of 6-month mortality
Rincon 2013 (79)	USA	Cohort	2003-2008	TBI	1212	+	Arterial hyperoxia was independently associated with higher in-hospital case fatality
Jeon 2014 (80)	USA	Cohort	1996-2011	Stroke	252	+	Exposure to hyperoxia was associated with delayed cerebral ischemia
Rincon 2014 (81)	USA	Cohort	2003-2008	Stroke	2894	+	Arterial hyperoxia was independently associated with in-hospital death as compared with either normoxia or hypoxia
Roffe 2011 & Ali 2013 (82, 83)	UK	RCT pilot	2004-2008	Stroke	289	-	Routine oxygen supplementation started within 24 h of hospital admission with acute stroke led to a small improvement in neurological recovery at 1 week, but no outcome differences were observed at 6 months
Rønning 1999 (84)	NOR	Quasi-RCT	1994-1995	Stroke	310	+	Supplemental oxygen should not routinely be given to nonhypoxic patients with minor or moderate strokes
Singhal 2005 (85)	USA	RCT pilot	NA	Stroke	16	-	High-flow oxygen therapy is associated with a transient improvement of clinical deficits and MRI abnormalities

Table 1. (continued)

Author	Country	Study type	Inclusion period	Subgroup	Sample size	Harm	Conclusions
Young 2012 (86)	ANZ	Cohort	2000-2009	Stroke	2643	-	Worst arterial oxygen tension in the first 24h was not associated with outcome
Stolmeijer 2014 (87)	NET	Cohort	NA	Sepsis	83	-	No association between mortality and hyperoxia, nor between lower FiO_2 and other detrimental effects

+, study found harm from supplemental oxygen or arterial hyperoxia; -, no harm found from supplemental oxygen or arterial hyperoxia.
ACS, Acute coronary syndrome; ADHF, Acute decompensated heart failure; AMI, Acute myocardial infarction; ARDS, Acute respiratory distress syndrome; CA, Cardiac arrest; CO2, Carbon dioxide; COPD, Chronic obstructive pulmonary disease; FiO2, Fraction of inspired oxygen; ICU, Intensive care unit; MRI, Magnetic resonance imaging; NA, Not available; PaO2, Partial pressure of arterial oxygen; PCI, Percutaneous coronary intervention; MV, Mechanical ventilation; PEEP, Positive end-expiratory pressure; RCT, Randomized Controlled Trial; SpO2, Oxyhemoglobin saturation; STEMI, ST-segment elevation myocardial infarction; TBI, Traumatic brain injury

As highlighted in recent meta-analyses (88, 89), the effects on major clinical end points are conflicting and may be partially explained by heterogeneous methodology and subgroup differences in critically ill patients. Pooled effect estimates favoring normoxia are quite consistent but the harmful effects were previously shown to be impacted by the definition of hyperoxia and may be more pertinent to specific subgroups and at specific moments of admission.

It is well-established that the use of higher FiO_2 can lead to progressive hypercapnia during a state of chronic compensated respiratory acidosis and serious adverse outcomes have been shown in acute exacerbations of chronic obstructive pulmonary disease (COPD) or asthma (54-56). Likewise, high fractions of oxygen in the inspired air and arterial blood have been associated with increased mortality in mechanically ventilated patients (52).

Owing to a striking lack of robust clinical trials, a causal relationship is still uncertain and both the magnitude and direction of the associations depend on the adjustment for illness severity scores, FiO_2 and other confounders (51, 52). Future randomized controlled studies are urgently needed to definitively elucidate the causal effects of oxygenation targets and derangements on clinical outcomes of critically ill patients.

Excessive oxygenation may be most intensively studied after resuscitation from cardiac arrest as both the vascular alterations and the ischemia and reperfusion injury are hypothesized to be hazardous (90). In a dose-dependent manner, hyperoxia has been linked to worse outcome in these patients. (58, 60-62). The adverse association was not systematically reproduced, possibly due to heterogeneity in study methods (57, 59, 64, 66, 67, 91). The only randomized controlled trial in the postresuscitation period found that 30% oxygen ventilation was not worse in comparison with 100% oxygen, but the study was underpowered to detect significant differences (63). In view of all recent data, supplemental oxygen administration during resuscitation still appears desirable, while hyperoxia should be avoided in the post-resuscitation phase and saturation should be targeted at 94–96% (90, 92).

A large number of both experimental and clinical studies have primed pediatricians with great awareness of the risks of hyperoxia. For neonatal resuscitation, the routine use of 100% oxygen has been abandoned after numerous associations with myocardial, neurologic and kidney injury, retinopathy, inflammation and increased mortality (93, 94). However, strict adherence to lower target ranges of oxygen saturation among preterm infants did not significantly reduce disability or deaths (95). Results from a prospective large-scale meta-analysis investigating the most appropriate level of oxygenation for extremely preterm neonates suggested that functional oxyhemoglobin saturation (SpO_2) should be targeted at 90-95% in the postnatal period (96).

Hyperoxia-induced vasoconstriction poses a major concern in the management of acute coronary syndromes and guidelines increasingly suggest a restriction of supplementary oxygen to only those at increased risk for hypoxia (97). Indeed, oxygen therapy has not been shown to be beneficial after acute myocardial infarction and may even be harmful causing a marked reduction in coronary blood flow and myocardial oxygen consumption (98, 99). The vasoconstriction caused by hyperoxia may be of special concern in the acute setting before reperfusion. The AVOID trial aimed to definitively qualify the role of supplemental oxygen in acute myocardial infarction (70) and found increased myocardial injury, recurrent myocardial infarction, cardiac arrhythmia and

infarct size at six months (100). In contrast, a smaller trial observed a beneficial effect of 30-40% oxygen inhalation over controls both during occlusion and reperfusion (72). Hemodynamic effects may also be pertinent to patients with acute ischemic stroke, who do not appear to benefit from increased survival after prolonged treatment with oxygen (82, 84).

Despite the theoretical benefit of decreasing intracranial pressure through cerebral vasoconstriction, hyperoxia has repeatedly been associated with delayed cerebral ischemia and increased cerebral excitotoxicity after cerebrovascular incidents (77, 80, 81). Interestingly, the synergistic combination of hyperbaric and normobaric hyperoxia was recently found to have potential therapeutic efficacy in severe traumatic brain injury (101). However, observational data in patients with traumatic brain injury, ischemic stroke, subarachnoid or intracerebral hemorrhage, remain equivocal (74-76, 78, 79, 86).

Perioperative care

Liberal oxygen supply is usually accepted in perioperative care, in order to avoid potentially life-threatening consequences of hypoxia during surgery. Further effects of perioperative hyperoxia have been comprehensively summarized in meta-analyses, enrolling over 7,000 patients, and generally showed a reduced risk of surgical site infections and postoperative nausea, without luxation of postoperative atelectasis (102, 103). However, risks may outweigh benefits in specific age groups (39) and different subsets. This was recently highlighted in patients undergoing cancer surgery where 80% oxygen supply in the perioperative setting showed a significantly increased long-term all-cause mortality compared with those randomized to 30% (104).

Implications for therapy

Several therapeutic options that limit the harmful effects of hyperoxia can be contemplated, but prevention of excessive oxygenation is likely to be the most effective strategy. A rational approach may be a more conservative administration strategy in which oxygen is titrated to a lower tolerable level in order to prevent iatrogenic harm while preserving adequate tissue oxygenation. Recently, a pilot interventional study showed that conservative oxygen therapy in mechanically ventilated patients in the intensive care unit (ICU) can be feasible and free of adverse outcomes, while decreasing excess oxygen exposure (53). Importantly, when the risks for severe tissue hypoxia are pronounced, ample oxygen supply remains vital and should be started immediately to increase oxygen delivery and preserve tissue oxygenation. Also, oxygen may aid hemodynamic stabilization, decrease intracranial pressure and can be used to stimulate erythropoietin and increase hemoglobin, when using intermittent hyperoxia as a paradoxical trigger for HIF expression.

Experimental interventions to decrease harm from hyperoxia are targeted at numerous steps in the pathway of ROS-induced damage. The primary source for intervention in the oxidative cycle is inhibition of oxidant generation, either quantitatively or qualitatively. Bleomycin and amiodarone are well-known originators of drug-induced pulmonary disease and should be avoided to minimize preventable ROS formation (105, 106). Limiting the exposure to other exogenous stimuli or preventing electron leakage in the electron transport chain may protect the mitochondria,

but this strategy proves cumbersome in actual practice. Although the clinical applicability has been questioned due to little or no preventative or therapeutic effect, the supply of antioxidant enzymes may be a potentially feasible approach to facilitate the conversion, avoid the intermediate formation, and reduce the concentration of strongly reactive oxidants. However, some of these antioxidants may actually have pro-oxidant properties depending on their concentration and interaction with other molecules. The neutralizing effect of antioxidants may also not be sufficient to secure metabolic stability, even when secondary inflammation is mitigated. Finally, oxidant scavenging can shift the balance towards harm when the role of oxidants in cell signaling pathways is suppressed (107).

As an alternative, pathways of cell integrity, cell death, and inflammation may be targeted to reduce further damage and enhance the defense against oxygen radicals. Experimental research suggests protective effects through modulation of protein kinases (108, 109) and transcription factors (110-113). Moreover, numerous preclinical studies have demonstrated that manipulation of chemokines, cytokines (13, 114), growth factors (115), receptors (116-118) and DAMPs (11, 12, 119) may limit hyperoxia induced injury, but these targets all remain to be evaluated at the bedside.

CONCLUSION

Although oxygen remains of life-saving importance in critical care, accumulating evidence has demonstrated the prominent role of hyperoxia and the consequent formation of reactive oxygen species in the pathogenesis of several life-threatening diseases. The toxic effects of supraphysiological oxygen concentrations are driven by cell damage, cell death and inflammation. These aspects are of special concern in the pulmonary compartment, where absorption atelectasis impairs respiratory function at high inspiratory oxygen levels. The cerebral and coronary circulations are at specific risk when vascular alterations manifest. Long-term exposure to hyperoxia impairs the innate immune response and increases susceptibility to infectious complications and tissue injury. Given that critically ill patients are prone for inflammation, cardiovascular instability and depleted antioxidant mechanisms, the most rational practice may be to supply oxygen conservatively and titrate the therapy carefully to the patient's needs. However, our understanding of oxygen toxicity is limited in humans and conflicting findings hamper the constitution of compelling guidelines. Further research is warranted to study hyperoxia induced effects in clinical practice, to elucidate time- and dose-response relationships, and to provide evidence-based oxygenation targets and interventions through robust clinical trials.

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LIST OF ABBREVIATIONS

DAMP, damage-associated molecular pattern molecule; FiO_2, fraction of inspired oxygen; HIF, hypoxia-inducible factor; ICU, intensive care unit; PaO_2, partial pressure of arterial oxygen; PMN, polymorphonuclear neutrophil; ROS, reactive oxygen species

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3

HYPEROXIA PROVOKES A TIME- AND DOSE-DEPENDENT INFLAMMATORY RESPONSE IN MECHANICALLY VENTILATED MICE, IRRESPECTIVE OF TIDAL VOLUMES

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ABSTRACT

Background

Mechanical ventilation and hyperoxia have the potential to independently promote lung injury and inflammation. Our purpose was to study both time- and dose-dependent effects of supplemental oxygen in an experimental model of mechanically ventilated mice.

Methods

Healthy male C57Bl/6J mice, aged 9–10 weeks, were intraperitoneally anesthetized and randomly assigned to the mechanically ventilated group or the control group. In total, 100 mice were tracheotomized and mechanically ventilated for either 8 or 12 hours after allocation to different settings for the applied fractions of inspired oxygen (FiO_2, 30%, 50% or 90%) and tidal volumes (7.5 ml/kg or 15 ml/kg). After euthanisation arterial blood, bronchoalveolar lavage fluid (BALf) and tissues were collected for analyses.

Results

Mechanical ventilation significantly increased the lung injury score ($P<0.05$), mean protein content ($P<0.001$) and the mean number of cells ($P<0.01$), including neutrophils in BALf ($P<0.001$). In mice ventilated for 12 hours, a significant increase in TNF-α, IFN-γ, IL-1β, IL-10, and MCP-1 ($P<0.01$) was observed with 90% FiO_2, whereas IL-6 showed a decreasing trend (P for trend = 0.03) across FiO_2 groups. KC, MIP-2, and sRAGE were similar between FiO_2 groups. HMGB-1 was significantly higher in BALf of mechanically ventilated mice compared to controls and showed a gradual increase in expression with increasing FiO_2. Cytokine and chemokine levels in BALf did not markedly differ between FiO_2 groups after 8 hours of ventilation. Differences between the tidal volume groups were small and did not appear to significantly interact with the oxygen levels.

Conclusions

We demonstrated a severe vascular leakage and a pro-inflammatory pulmonary response in mechanically ventilated mice, which was enhanced by severe hyperoxia and longer duration of mechanical ventilation. Prolonged ventilation with high oxygen concentrations induced a time-dependent immune response characterized by elevated levels of neutrophils, cytokines and chemokines in the pulmonary compartment.

INTRODUCTION

Supplemental oxygen administration is essential to enhance survival in respiratory impaired and mechanically ventilated patients. Inspiratory fractions of oxygen (FiO_2) typically exceed concentrations of atmospheric air and are frequently applied for prolonged periods during mechanical ventilation in patients suffering from severe respiratory distress. However, both mechanical ventilation and hyperoxia can promote lung injury and induce adverse effects through diverse mechanisms. Clinical studies have retrospectively shown associations between arterial hyperoxia and poor outcomes during specific cardiovascular, neurological, respiratory and traumatic events (1-4). Accumulating evidence indicates a U-shaped survival curve of critically ill and mechanically ventilated patients in relation to arterial oxygen levels in the first 24 hours of admission (5-8).

Impaired lung function may be caused by the adverse hemodynamic effects that are mainly imputed to direct vasoconstrictive actions of high oxygen concentrations, and atelectasis which may be aggravated by local and systemic inflammatory responses. These responses have repeatedly been documented in rodents following hyperoxic exposure in inhalation chambers (9-15). Although hyperoxia has been suggested to induce time-dependent inflammatory responses (10), studies in animals are usually restricted to periods of up to 6 hours of mechanical ventilation, limiting its clinical applicability (16-19). Furthermore, the interaction between mechanical ventilation and concurrent hyperoxia may transcend lung injury by alveolar distention alone (9, 17, 20-22). Given that oxygen therapy cannot altogether be avoided, we aimed to increase knowledge on the host response to different levels of oxygen. Hypothesizing that hyperoxia induces a dose-dependent gradual inflammatory response that may be aggravated by prolonged periods of mechanical ventilation, our purpose was to induce hyperoxia in mice and study both time- and dose-dependent inflammation effects of supplemental oxygen during prolonged ventilatory support with protective and injurious tidal volumes.

METHODS

The Animal Care and Use Committee of the Academic Medical Center of the University of Amsterdam, the Netherlands approved the study protocol in accordance with applicable research and ethical protocols. Animal procedures were performed in consistence with Institutional Standards for Care and Use of Laboratory Animals.

Animals

Healthy male C57Bl/6J mice were obtained from Charles River (Maastricht, the Netherlands) and housed in a temperature- and light-controlled room. The animals were acclimatized at the animal facility for at least seven days and had free access to rodent chow and water. Animal welfare was warranted throughout the experiment (23). Conscious animals were injected twice for intraperitoneal prehydration and anesthesia induction. Thereafter, mice were regularly checked on pain stimuli and discomfort. The titration scheme for adequate anesthesia was determined in pilot experiments.

Design

At baseline, 109 mice aged 9–10 weeks (20–28 g) were intraperitoneally prehydrated with a bolus of 1 ml normal saline and randomly assigned to the mechanical ventilation (MV) group (n=100) or the control group (n=9). All mice in the MV group were randomized to subgroups (n = 8–9 per subgroup) by allocating different settings for the applied fractions of inspired oxygen (FiO_2 = 30%, 50% or 90%), tidal volumes (TV = 7.5 ml/kg or 15 ml/kg) and MV duration (8 or 12 hours). The control group mice were spread over multiple days along with the instrumentation of the MV groups during the whole experimental period.

Experimental procedures have been described in detail previously (24, 25). One hour after prehydration, mice assigned to the MV groups (n=8–9 per group), were anesthetized with a 0.15-0.21 ml intraperitoneal bolus of 126 mg/kg ketamine (Eurovet Animal Health BV, Bladel, the Netherlands), 0.1 mg/kg dexmedetomidine 0.5 mg/ml (Elanca Animal Health, Houten, the Netherlands), 0.5 mg/kg atropine sulfate (Centrafarm BV, Etten-Leur, the Netherlands) and 5 ml/kg 0.9% saline. Maintenance anesthesia was injected hourly through an intraperitoneal catheter (PE 10 tubing, BD, Breda, the Netherlands) and consisted of 36 mg/kg ketamine, 0.02 mg/kg dexmedetomidine, 0.075 mg/kg atropine sulfate and 9.45 ml/kg 0.65% saline. A 1:5 mix of 0.65% saline and 8.4% sodium bicarbonate was intraperitoneally administered through the catheter every 30 minutes in order to compensate for fluid loss and maintain physiological bicarbonate levels (25). Body temperature was strictly controlled between 36.5 and 37.5°C. Systolic blood pressure and heart rate were noninvasively measured using a murine tail pressure cuff with pulse transducer and monitored on a data acquisition system (LabChart, ADInstruments Ltd, Oxford, United Kingdom). Tidal volumes were monitored using a calibrated pneumotachometer (tracheal cannula OD=1.3 mm, PTM type 378/0.9, HSE-Harvard Apparatus GmbH, March-Hugstetten, Germany) and respiration data acquisition software (BDAS, HSE-Harvard Apparatus GmbH).

Anesthetized mice were tracheotomized and a Y-tube connector (OD 1.0 mm, ID 0.6 mm) was surgically inserted in the trachea and fixed above the carina. Subsequently, animals were placed on a heating plate in supine position and connected to the ventilator (Babylog 8000 plus, Dräger Medical, Lübeck, Germany). Ventilator settings were pre-determined in pilot experiments and targeted at normal acid-base balance (24). Ventilators were pressure-controlled and set to deliver low tidal volumes (LTV, 7.5 ml/kg) or high tidal volumes (HTV, 15 ml/kg). In both ventilation strategies, positive end-expiratory pressure (PEEP) levels were set at 3 cmH_2O and the inspiration to expiration ratio at 1:2.8. Respiratory rates were controlled at 160 (LTV) or 52 (HTV) breaths per minute. Recruitment maneuvers were performed every 30 (LTV) or 60 (HTV) minutes by means of inspiratory holds with a pressure of 20 mbar during 5 seconds.

Immediately after randomization, ventilators were adjusted to the assigned settings by an independent biotechnician. Inspiratory pressures were adjusted and regulated to achieve appropriate TV throughout the experiment. At the end of the experiment ventilated mice were euthanized by withdrawing blood from the carotid artery. Researchers were blinded for administered FiO_2 levels during the experimental procedures. The allocation code of randomization was supplied by the time all data and assay results were collected.

Measurements

After euthanisation arterial blood was collected in heparin-coated syringes and used for blood gas analysis (Rapidpoint 405, Siemens Healthcare, Tarrytown, NY, USA). Lungs were resected en bloc and the right lung was instilled with normal saline (3x 0.5 mL) to obtain bronchoalveolar lavage fluid (BALf), which was used for automated cell counting (Z2 Beckman Coulter Counter, Brea, USA). Differential counts were performed on Giemsa stained cytospin slides. BALf was centrifuged and the supernatant was stored at -80°C for assessment of protein levels and cytokines. The left lung was weighed and thereafter fixed in 4% formalin and embedded in paraffin. Lung sections were stained with hematoxylin eosin (H&E) to analyze lung histopathology. A dedicated pathologist determined the histopathological lung injury score on a nominal scale by the sum of the score for four pathologic parameters: edema, haemorrhage, interstitial cell infiltration and hyaline membranes as described previously (24). Relative lung weight, expressed as lung weight corrected for total body weight at baseline, was used as surrogate for lung tissue edema.

Cytokines (IL-1β, IL-6, IL-10, MCP-1, MIP-2, KC, TNF-α, IFN-γ) were measured in BALf by Luminex (Merck Millipore Chemicals BV, Amsterdam, The Netherlands). High mobility group box 1 (HMGB-1, IBL International BV, Amersfoort, The Netherlands) and the soluble receptor for advanced glycation end products (sRAGE, R&D Systems, Abingdon, UK) were determined by enzyme-linked immunosorbent assays (ELISA) according to the manufacturer's protocols. Total protein levels were determined in serum and BALf (Oz Biosciences, Marseille, France), using bovine serum albumin as reference.

The right lung was used for total RNA isolation from tissue homogenates (RNA-Bee, Tel-Test Inc, Bio-Connect BV, Huissen, the Netherlands), first-strand cDNA synthesis (SuperScript Choice System, Life Technologies, Breda, the Netherlands) and real-time quantitative PCR (TNF-α, IL-6, MMP-12, MCP-1, TF, PAI-1), using β-actin as a housekeeping gene reference, were performed on a LightCycler 480 (Roche, Almere, the Netherlands) of the Leiden Genome Technology Center (Leiden, The Netherlands) as described previously (26).

Statistical analysis

The partial pressure of arterial oxygen (PaO_2) at the end of the experiment was defined as the primary outcome. Inflammatory markers and markers of lung injury were assessed as secondary outcomes. Based on previous pilot results and with a group size of 8 animals per group the Wilcoxon ranksum test ensures 80% power using a two sided significance level of 0.05 to detect an estimated effect size of 1.85 that the observed parameter differs between groups. With an anticipated dropout rate of one per group, nine animals were initially assigned to each group. Differences between study groups were tested with one-way analysis of variance or Kruskal Wallis as appropriate. Cuzick's test was used to test for trends across different FiO_2 groups. Statistical analyses were performed using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and STATA/SE 10.1 (StataCorp LP, College Station, TX, USA).

RESULTS

All mice survived mechanical ventilation with the applied settings in a volume-targeted approach (Table 1). Median systolic blood pressures decreased gradually during 8 or 12 hours of mechanical ventilation 145 mmHg to 90 mmHg) and were slightly higher in the 90% FiO_2 group (Table 1, Additional file 1 Figure S1). Heart rates and body temperatures remained stable throughout the experiment.

Oxygenation and ventilation

The partial pressure of oxygen in the carotid arterial blood at the end of mechanical ventilation was distinctly higher with increasing fractions of supplied oxygen (P<0.001, Fig. 1a). $PaCO_2$ was in general lower for the HTV groups, but did not show a trend across FiO_2 groups (Fig. 1b). The PaO_2/FiO_2 ratio decreased for mechanically ventilated mice in comparison to controls and was markedly higher for HTV groups after 12 hours of mechanical ventilation (Fig. 1c). Dynamic lung compliance decreased gradually over the study interval for all study groups but the decrease was nearly complete after three hours of mechanical ventilation and was larger for the HTV groups (Fig. 1d).

Markers of lung injury

Mechanical ventilation significantly increased the lung injury score (Fig. 2a, 1.6-fold at 8 hours, P<0.01; and 1.5-fold at 12 hours, P<0.05), mean protein content (Fig. 2b, 2.6-fold at 8 hours, P<0.001; and 2.2-fold at 12 hours, P<0.001) and the mean number of cells (Fig. 2c, 1.7-fold at 8 hours, P<0.01; and 2.0-fold at 12 hours, P<0.001), including neutrophils in BALf (Fig. 2d, 132-fold at 8 hours, P<0.001; and 180-fold at 12 hours, P<0.001), demonstrating vascular leakage and inflammation as a result of mechanical ventilation even at relatively low hyperoxic conditions of 30% FiO_2 and low tidal volumes. Increased hyperoxia up to 90% FiO_2 did not further increase protein content or the total number of cells in BALf, but showed an increased trend in the percentage of neutrophils towards higher FiO_2 levels (P for trend = 0.03). Histopathology showed a decrease in

Table 1. Ventilation and hemodynamic parameters

	8h			12h		
	30%	**50%**	**90%**	**30%**	**50%**	**90%**
LTV						
TV (µl)	181 (0)	182 (0)	179 (0)	176 (0)	178 (1)	176 (0)
P_{insp} (mbar)	13 (0)	14 (0)	12 (0)	12 (0)	13 (0)	12 (0)
SBP (mmHg)	116 (7)	128 (7)	123 (5)	103 (4)	102 (5)	112 (4)
HTV						
TV (µl)	351 (0)	379 (1)	372 (1)	366 (2)	371 (1)	360 (1)
P_{insp} (mbar)	20 (0)	21 (0)	20 (0)	20 (0)	20 (0)	20 (0)
SBP (mmHg)	114 (6)	136 (8)	124 (7)	104 (4)	110 (6)	113 (5)

Data are means ±SD. TV, tidal volume; P_{insp}, inspiratory pressure; SBP, systolic blood pressure. All indicated parameters were measured hourly.

air restraint, suggesting progressive alveolar collapse, with higher oxygen levels (Additional file 1 Figure S2), but this was not translated in a significant difference in the lung injury score between the different FiO_2 groups (Fig. 2a).

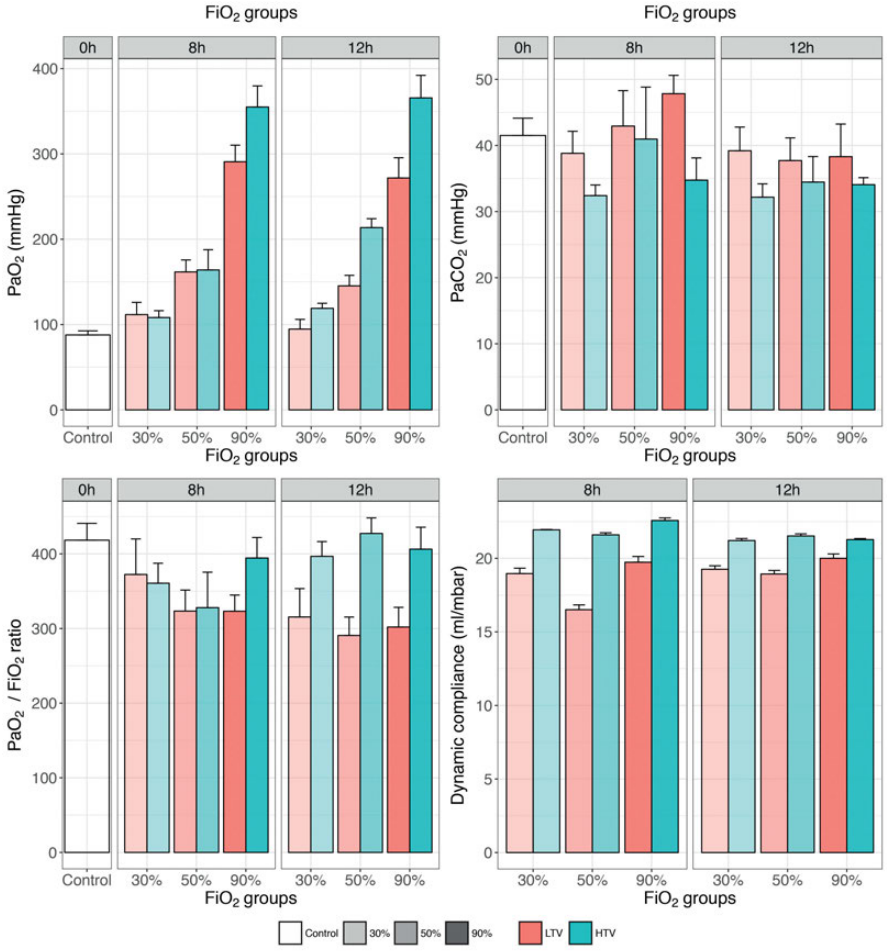


Figure 1. Arterial oxygenation and ventilation parameters.
Data are means ±SEM. Arterial oxygenation in carotid blood (1a, upper left panel), arterial carbon dioxide in carotid blood (1b, upper right panel), PaO_2/FiO_2 ratio (1c, lower left panel) and dynamic compliance (1d, lower right panel). Facets within the panels represent mechanical ventilation time. Different colors represent different tidal volume groups and different transparency levels represent different FiO_2 groups. 0h, no mechanical ventilation time (control group); 8h, 8 hours of mechanical ventilation; 12h, 12 hours of mechanical ventilation. LTV, low tidal volumes; HTV, high tidal volumes. Dynamic lung compliance (tidal volume size / (peak inspiratory pressure – PEEP) was measured hourly. PaO_2 and $PaCO_2$ were measured once in the arterial blood gas sample taken from the carotid artery at the end of the experiment.

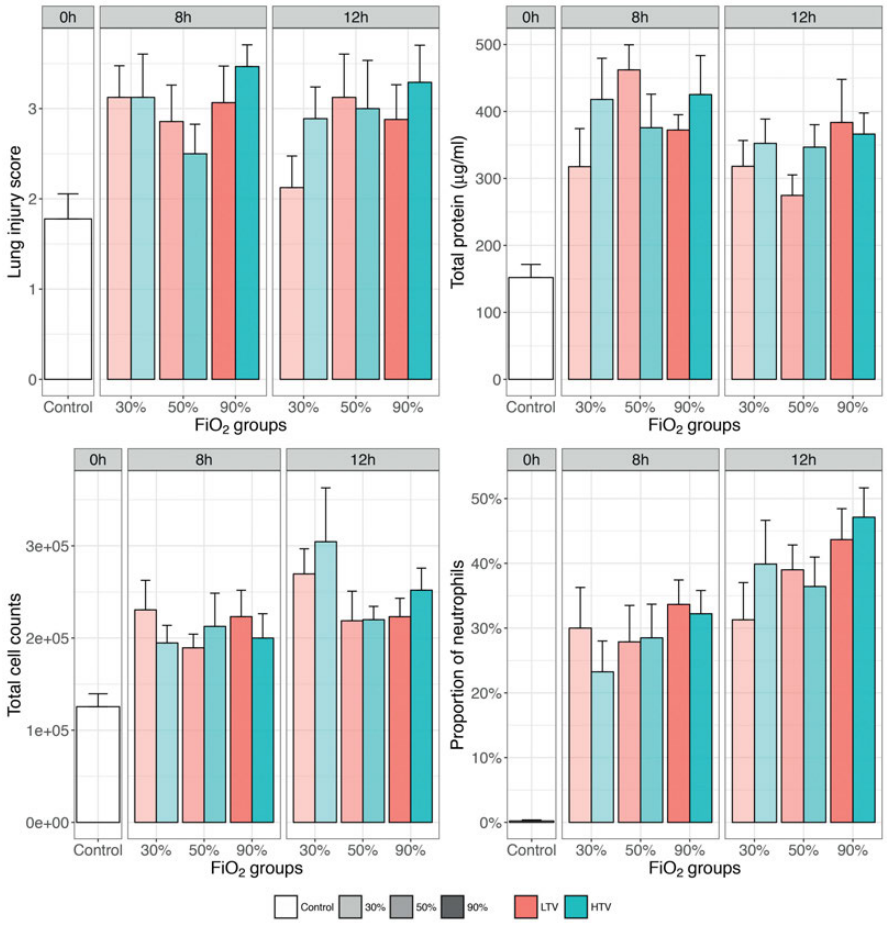


Figure 2. Markers of lung injury in BALf after indicated study interval.
Data are means ±SEM. Lung injury score (2a, upper left panel), total protein content (2b, upper right panel), total cell counts (2c, lower left panel) and proportion of neutrophils (2d, lower right panel) in BALf obtained after the study interval. Facets within the panels represent mechanical ventilation time. Different colors represent different tidal volume groups and different transparency levels represent different FiO_2 groups. 0h, no mechanical ventilation time (control group); 8h, 8 hours of mechanical ventilation; 12h, 12 hours of mechanical ventilation. LTV, low tidal volumes; HTV, high tidal volumes.

Markers of inflammation

Cytokine and chemokine levels in BALf increased at 8 and 12 hours after mechanical ventilation, but did not markedly differ between FiO_2 groups at 8 hours of ventilation (P for trend > 0.05, Additional file 1 Figure S3). In mice ventilated for 12 hours, a significantly increasing trend in TNF-α, IFN-γ, IL-1β, IL-10, and MCP-1 (Fig. 3, P for trend < 0.01) was observed with increasing FiO_2, whereas IL-6 showed a decreasing trend (P for trend = 0.03). KC, MIP-2, and sRAGE were similar between FiO_2 groups. HMGB-1 was significantly higher in BALf of mechanically ventilated mice compared to controls and

showed a gradual increase in expression with increasing FiO_2. Almost no differences in cytokine and chemokine levels in the BALf were observed between the 30% and 50% oxygen groups.

Differences between the tidal volume groups were small (Additional file 1 Figure S4) and did not appear to significantly interact with the oxygen levels (P>0.50 for the interaction term for each inflammatory mediator, except for IL-6, P=0.03). Inflammatory markers were also measured at 12 hours of mechanical ventilation in the serum and are shown in Additional file 1 Figure S5.

The RNA expression of selected markers showed an increased relative expression of TNF-α, IL-6, and MCP-1 in lung homogenate of mice that were mechanically ventilated with high tidal volumes compared to controls (Additional file 1 Figure S6)

DISCUSSION

In this experimental study, we demonstrated a severe vascular leakage and a pro-inflammatory pulmonary response in mechanically ventilated mice, which was enhanced by severe hyperoxia and longer duration of mechanical ventilation. Prolonged ventilation with high oxygen concentrations induced a time-dependent immune response characterized by elevated levels of neutrophils, cytokines and chemokines in the pulmonary compartment.

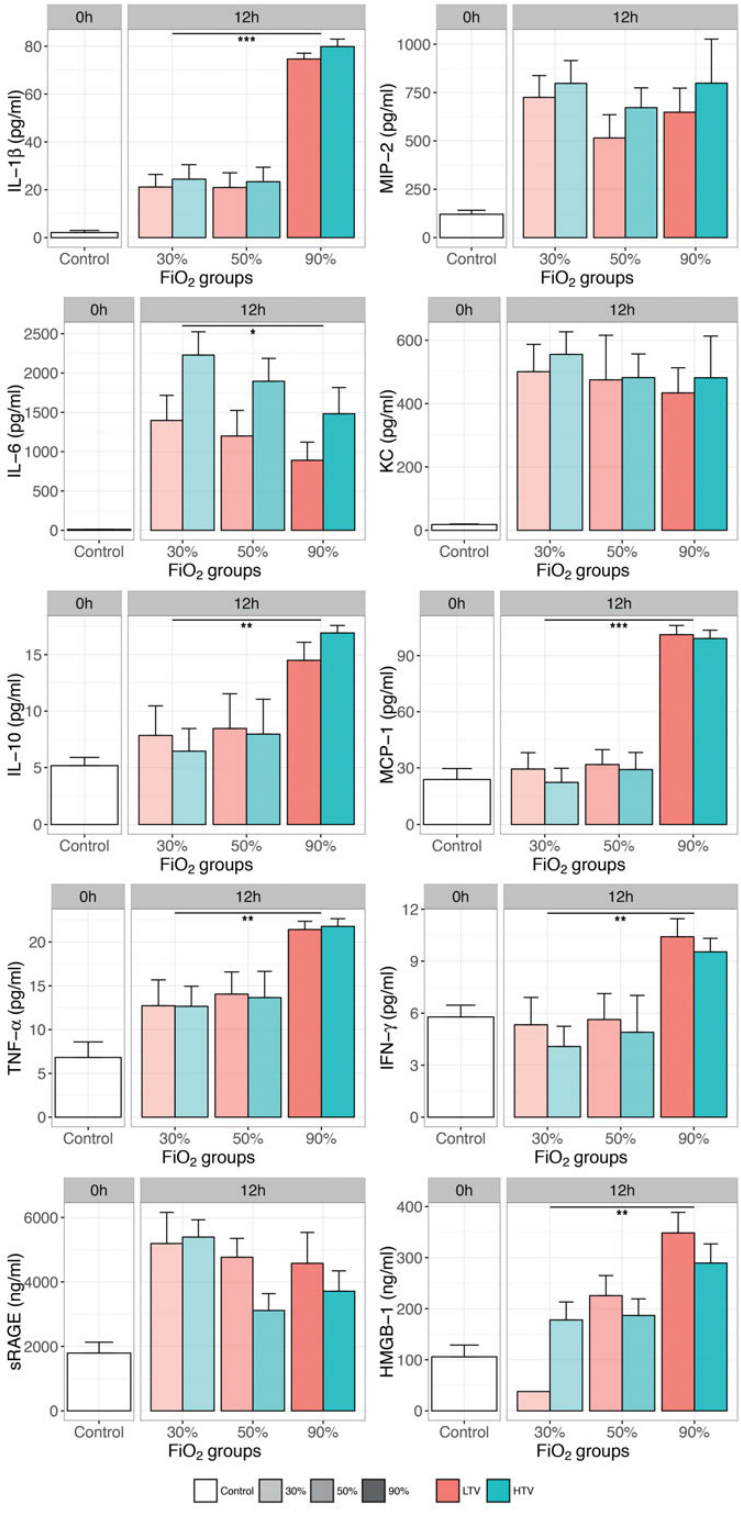
Although most studies in mechanically ventilated animals are restricted to short exposure periods, recent experiments in mechanically ventilated rodents, rabbits, and pigs, mimicking the clinical environment of critically ill patients, showed that hyperoxia serves as an important cofactor in acute lung injury, bacterial dissemination, progression of multiple system organ dysfunction and lethality (13-15), but can also improve organ function and attenuate tissue apoptosis during shock (27). In our study, divergent effects were observed in the expression of selected inflammatory markers across the experimental groups, which may be explained by the complex kinetics and dynamics of the immune response due to the concurrent exposure to anesthesia, mechanical ventilation and hyperoxia. Interaction between pro- and anti-inflammatory cytokines may contribute to the differences in cytokine levels in the experimental groups. Rapid upregulation of TNF-αwas seen even in the acute phase reaction after induction of anesthesia in control mice. Cytokine concentrations may decrease after long-term hyperoxic exposure and a fast upregulation of inflammatory action can be followed by a gradual impairment or suppression of the innate immune system (28), which may in turn make the lung more susceptible to injury and infection. Differences in cytokine levels between the FiO_2 groups were relatively mild. We observed a strong inflammatory effect at very high oxygen concentrations (FiO_2 90%) while the increase from 30% to 50% did not make a large difference. Indeed, 50% of inspired oxygen may not be as detrimental as 90% as evidenced by the clear increase in neutrophils and most cytokines during 90% oxygen administration, which was also described in other studies (29-32). In addition, ventilation with 30% may actually be a model of relative tissue hypoxia in mice following progressive lung injury during the experiment, although this was not reflected by the PaO_2 levels. Comparison with control groups suggests that mechanical ventilation itself was very harmful, possibly not allowing additional damage by increasing oxidative stress. Both hypoxia and hyperoxia may induce oxidative stress and relative changes in hyperoxia may trigger upregulation of the hypoxia inducible factor (HIF) (33).

Figure 3. Inflammatory mediators in BALf in controls and after 12h of mechanical ventilation. Cytokine and chemokine levels in BALf obtained after 12 hours of mechanical ventilation. Data are means ±SEM. Facets within the panels represent mechanical ventilation time. Different colors represent different tidal volume groups and different transparency levels represent different FiO_2 groups. 0h, no mechanical ventilation time (control group); 12h, 12 hours of mechanical ventilation. LTV, low tidal volumes; HTV, high tidal volumes. Cuzick's P for trend in increasing oxygen levels at 12 hours of mechanical ventilation: IL-1β, <0.001; MIP-2, 0.27; IL-6, 0.03; KC, 0.22; IL-10, 0.001; MCP-1, <0.001; TNF-α, 0.001; IFN-γ, 0.001; sRAGE, 0.11; HMGB-1, 0.001. * P for trend <0.05; ** P for trend <0.01; *** P for trend <0.001.

Furthermore, damage associated molecular pattern (DAMP) molecules play a key role in the inflammatory response to injury and have been suggested to modulate the effects of hyperoxia and oxidative stress (34, 35). In this matter, HMGB-1 has been described as the archetypal chemokine that is upregulated by the innate immune system in response to cell stress (36). We also observed increased levels of this protein in the lungs of mechanically ventilated mice, particularly after concurrent exposure to high FiO_2. The overall protein content did not significantly increase with severe hyperoxia, but this interpretation may be limited as we did not correct the protein in BALf for urea (epithelial lining fluid). The expression of most cytokines in BALf was not essentially different than in the serum, which may be a result of extended duration of mechanical ventilation causing systemic inflammation. In line with previous experiments the presence of cytokines with short term ventilation was definitely more pronounced in the pulmonary compartment compared to circulating blood of rodents (25, 37).

Our study and others generated conflicting data regarding the inflammatory response after hyperoxic ventilation describing both pro- (15, 17, 38, 39) and anti-inflammatory (40, 41) responses. Kiers et al. recently demonstrated that, in the absence of systemic inflammation, short-term hyperoxia without mechanical ventilation does not result in increased levels of inflammatory cytokines, neutrophil phagocytosis nor ROS generation in both mice and healthy volunteers (42). In the present study, the expression of inflammatory markers was shown to be divergent after mechanical ventilation and with increasing FiO_2, which is consistent with previous research (16). Bailey et al. concluded that prolonged mechanical ventilation of healthy rat lungs with a physiological strategy can contribute to the inflammatory response and cause alterations to pulmonary surfactant (43). Lung injury due to continuous hyperoxic exposure has also been shown to be dose-dependent in rats (12, 15).

Some clinical scenarios may dictate non-protective ventilation, both with high pressures and high levels of inspired oxygen in patients with heavily injured lungs. However, it is not exactly known whether this combination works synergistically in causing lung injury. Our data do not imply such an 'add-on effect', but the discrepancy with a previous study (20) may be explained by the use of lower tidal volumes in our study. It is also possible that the extended duration of mechanical ventilation alone was enough to cause ventilator-induced lung injury (VILI) without an additional effect of tidal volume size. An alternative explanation may be that lower respiratory rates compensated for high tidal volumes, while higher respiratory rates increased the risk of lung


0h
12h
IL–1β (pg/ml)
MIP–2 (pg/ml)
IL–6 (pg/ml)
KC (pg/ml)
IL–10 (pg/ml)
MCP–1 (pg/ml)
TNF–α (pg/ml)
IFN–γ (pg/ml)
sRAGE (ng/ml)
HMGB–1 (ng/ml)
Control
30%
50%
90%
FiO2 groups
LTV
HTV

injury in the lower tidal volume groups. Also, some of the deleterious properties of hyperoxia may be overcome by applying PEEP, as it may counteract alveolar collapse from progressive nitrogen washout and mitigate the effects of atelectrauma (44).

In our study, lung injury scores did not reveal any histopathological difference between study groups. However, in previous work using a high tidal volume strategy with zero PEEP, total histopathology scores were shown to be higher compared to low tidal volumes and 3 cmH_2O PEEP with a marginal additive effect of ventilation duration (24). This was in accordance with a study reporting that pre-exposure to hyperoxia increases the susceptibility to VILI before initiation of mechanical ventilation (22). Others documented that short-term exposure to levels of oxygen up to 100% does not increase the changes in respiratory system mechanics induced by mechanical ventilation (16). The progressive airway collapse and inflammation with increasing FiO_2 may not have been severe enough to induce histopathological changes and affect lung function in our model. The striking heterogeneity that exists between experimental studies may be explained by differences in subjects (e.g. species, strains, genetical modification, age, sex), and exposure (e.g. pre-exposure, severity, duration, anesthesia, ventilation).

Although the experiments were performed according to the high standards for methodological quality of animal research (45), several limitations may apply to our experimental procedures. The lavage technique of the lungs may induce subtle differences in the dilution of returned fluid, although saline injection volumes were standardized. Storage of biological specimens was secured according to high quality protocols. Our analyses were restricted to specific features of injurious ventilation and hyperoxia, yet other underlying mechanisms affecting reactive oxygen species and mitochondrial damage have not been considered. Other covariates such as $PaCO_2$ may have influenced the results, even though this cannot be seen separate from ventilation settings and was inherent to adjusting tidal volumes and FiO_2. Furthermore, low respiratory rates, especially in the LTV group, are subphysiological for mice and may cause relative hypercapnia.

The experimental setting may hamper translation of study results to the clinical setting. Indeed, smaller species, such as mice have different lung mechanics and immune reactions than humans (46, 47). Healthy mice may also respond differently than critically ill patients, especially in case of injured lungs prior to the start of mechanical ventilation. Interestingly, moderate hyperoxia in mechanically ventilated patients without severe respiratory failure does not appear to increase systemic or pulmonary inflammation (48).

Further, the C57Bl/6J type mice that we used are the most widely used strain of mice for experimental research, but have been shown to carry a spontaneous mutation, which can result in mitochondrial redox abnormalities and may influence the functionality of the hyperoxia defense (49).

Strengths of this study include the prolonged duration of mechanical ventilation which may be representative of the intensive care unit (ICU) setting, where hyperoxia acts as a second hit on top of VILI. Indeed, we showed that the immune response was considerably stronger at 12 hours of mechanical ventilation compared to 8 hours, which may imply that models applying mechanical ventilation for extended duration more accurately reflect the underlying mechanisms and long-term effects. Demonstrable lung injury may follow the inflammatory response even later than

after 12 hours of hyperoxic mechanical ventilation. As such, our results further accentuate that we should limit the exposure to supraphysiological oxygen levels from excessive oxygen supply when prolonged periods of mechanical ventilation are anticipated.

CONCLUSION

Prolonged experimental hyperoxic mechanical ventilation was associated with a significant inflammatory response in the lung as evidenced by an influx of neutrophils in the pulmonary compartment and upregulation of specific inflammatory markers, which was not directly translated into extensive tissue lung injury or a change in lung compliance. The present experimental data may aid to determine optimal ventilator strategies in mechanically ventilated patients, but the dynamics and kinetics of hyperoxic ventilation need further exploration in order to characterize the long term effects and investigate protective measures.

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LIST OF ABBREVIATIONS

BALf, bronchoalveolar lavage fluid; DAMP, damage associated molecular pattern; ELISA, enzyme-linked immunosorbent assays; FiO_2, fraction of inspired oxygen; HIF, hypoxia inducible factor; HMGB-1, high mobility group box-1; HTV, high tidal volume; ICU, intensive care unit; IFN-γ, Interferon-γ; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-10, Interleukin-10; KC, Kupffer Cell; LTV, low tidal volume; MCP-1, Monocyte Chemoattractant Protein-1; MIP-2, Macrophage Inflammatory Protein-2; MV, mechanical ventilation; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; sRAGE, soluble Receptor for Advanced Glycation End products; TNF-α, Tumor Necrosis Factor-α; TV, tidal volume; VILI, ventilator-induced lung injury

ONLINE SUPPLEMENT

For the online supplement (**Additional file 1)**, please use the following weblink, or scan the QR-code with your mobile device

Additional file 1. https://static-content.springer.com/esm/art%3A10.1186%2Fs40635-017-0142-5/MediaObjects/40635_2017_142_MOESM1_ESM.docx. **Figure S1.** Mean systolic blood pressure over the study interval. **Figure S2.** Microscopic histopathology of representative mouse lung sections after 12 h of mechanical ventilation (H&E staining, ×10 magnification). **Figure S3.** Inflammatory mediators in BALf after 8 h of mechanical ventilation. **Figure S4.** Inflammatory mediators in BALf after study interval by tidal volume size. **Figure S5.** Inflammatory mediators in serum after 12 h of mechanical ventilation. **Figure S6.** Relative RNA expression of inflammatory markers in lung homogenate after 12 h of mice that were mechanically ventilated with high tidal volumes compared to controls.

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Part II

CLINICAL EFFECTS AND ASSOCIATED OUTCOMES

4

HEMODYNAMIC EFFECTS OF SHORT-TERM HYPEROXIA AFTER CORONARY ARTERY BYPASS GRAFTING

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ABSTRACT

Background

Although oxygen is generally administered in a liberal manner in the perioperative setting, the effects of oxygen administration on dynamic cardiovascular parameters, filling status and cerebral perfusion have not been fully unraveled. Our aim was to study the acute hemodynamic and microcirculatory changes before, during and after arterial hyperoxia in mechanically ventilated patients after coronary artery bypass grafting (CABG) surgery.

Methods

This was a single-center physiological study in a tertiary care ICU in the Netherlands. Twenty-two patients scheduled for ICU admission after elective CABG were enrolled in the study between September 2014 and September 2015.

In the ICU, patients were exposed to a fraction of inspired oxygen (FiO_2) of 90% allowing a 15-minutes wash-in period. Various hemodynamic parameters were measured using direct pressure signals and continuous arterial waveform analysis at three sequential time points: before, during and after hyperoxia.

Results

During a 15-minutes exposure to a fraction of inspired oxygen (FiO_2) of 90%, the partial pressure of arterial oxygen (PaO_2) and arterial oxygen saturation (SaO_2) were significantly higher. The systemic resistance increased ($P<0.0001$), without altering the heart rate. Stroke volume variation and pulse pressure variation decreased slightly. The cardiac output did not significantly decrease ($P=0.08$). Mean systemic filling pressure and arterial critical closing pressure increased ($P<0.01$), whereas the percentage of perfused microcirculatory vessels decreased ($P<0.01$). Other microcirculatory parameters and cerebral blood flow velocity showed only slight changes.

Conclusions

We found that short-term hyperoxia affects hemodynamics in ICU patients after CABG. This was translated in several changes in central circulatory variables, but had only slight effects on cardiac output, cerebral blood flow and the microcirculation.

Clinical trial registration

Netherlands Trial Register: NTR5064

BACKGROUND

During and after coronary artery bypass grafting (CABG), patients are supported with mechanical ventilation and supplemental oxygen. Despite its lifesaving characteristics and key role in the treatment of vasodilatory shock, oxygen therapy may harbor considerable risks given the relationship between prolonged hyperoxia, lung injury and adverse outcome (1-5). The effects of supplemental oxygen may be even more pertinent during cardiovascular events considering the direct effects of high arterial oxygen concentrations on the vascular tone (6, 7). Arterial hyperoxia has the potential to alter hemodynamics and has been associated with adverse outcomes and mortality after cardiac arrest, myocardial infarction, stroke, brain injury and during mechanical ventilation (8-14), yet not during cardiopulmonary bypass (15, 16). It is well established that high oxygen concentrations induce vasoconstriction and increase the resistance of the systemic circulation. However, the effects on vital parameters may be diverse and the venous and arterial aspects of the circulation have not been clearly distinguished in previous studies. Furthermore, the microcirculation may react differently than systemic hemodynamics (17).

Achieving hemodynamic stabilization is an important clinical prerequisite for early extubation and dismissal from the intensive care unit (ICU) after cardiothoracic surgery. Any intervention that influences hemodynamics and blood flow to the bypassed myocardial territories may impact functional recovery and requires optimal fine-tuning to achieve the best outcome. Although oxygen is generally administered in a liberal manner in the perioperative setting, the unraveling of the effects of oxygen administration on dynamic cardiovascular parameters, filling status and cerebral perfusion may provide novel insights in the pathophysiological mechanisms involved in hyperoxic exposure. Our aim was to study the acute hemodynamic and microcirculatory changes during increased oxygen supply in mechanically ventilated ICU patients after CABG surgery.

METHODS

Participants

Adult patients with symptomatic coronary artery disease without recent myocardial infarction scheduled for ICU admission after coronary artery bypass surgery were screened for eligibility. Patients with congestive heart failure, severe arrhythmias, intracardiac shunts, extensive peripheral arterial occlusive disease, symptomatic pulmonary disease, aortic aneurysm and/or significant valvular disease were not considered for inclusion. Patients with signs of severe hemodynamic instability (e.g., rapid changes in vascular resistance, use of inotropic agents) during ICU admission were excluded. Study approval was granted by the local medical ethics committee (LUMC P14.046), and all patients signed informed consent. The study was registered with the Netherlands Trial Register, number NTR5064, registration date February 2015.

Measurements

Anesthesia during surgery was maintained with propofol and sufentanil. Ventilation was adjusted to achieve normocapnia. FiO_2 was 40%, and a positive end-expiratory pressure of 5 cm H_2O was applied. Directly after surgery, patients were admitted to the ICU and received standard

postoperative care. Continuous infusion of propofol and sufentanil was maintained for all patients, and no bolus medications (fluids, vasoactive or sedative agents) were administered.

Mean arterial blood pressure (MAP) was measured via a 20-G radial arterial catheter inserted by Seldinger technique. Central venous pressure (CVP) was measured with a central venous catheter inserted in the right internal jugular vein (MultiCath venous catheter, Vigon GmbH & Co, Aachen, Germany). Pressure transducers (PX600F, Edwards Lifesciences) for the arterial and central venous signals were referenced to the intersection of the anterior axillary line and the fifth intercostal space. The airway pressure was measured at the entrance of the endotracheal tube and balanced at zero level against ambient air. Standard electrocardiogram leads were used to monitor heart rate. Body temperature was measured using a rectal temperature probe.

Beat-to-beat values of cardiac output (CO), stroke volume, stroke volume variation (SVV), pulse pressure variation (PPV) and heart rate (HR) were obtained by Modelflow using continuous arterial waveform analysis as previously described (18, 19). Hemodynamics were also monitored by the LiDCO*plus* monitor (LiDCO Group Plc., London, UK).

Before starting the protocol, the mechanical ventilation in volume-controlled mode was switched to airway pressure release ventilation (APRV), with settings adjusted to achieve the same minute ventilation, which allows for external control of the ventilator (Evita 4, Dräger AG, Lübeck, Germany). A computer program was used to control the ventilator as described previously (20). During the study interval, all patients were hemodynamically stable and ventilator settings, sedation and vasoactive therapy remained unchanged.

At least three videos of ten sequences (40 frames each) visualizing different sites of the sublingual microcirculation were recorded per patient per time point by the same dedicated researcher using sidestream dark field (SDF) imaging with the MicroScan Video Microscope (MicroVision Medical BV, Amsterdam, The Netherlands). The three best quality videos from representative multiple site imaging were analyzed, and calculated parameters were averaged. Previously suggested key points for optimal image acquisition were considered, and maximal efforts were undertaken to avoid pressure artifacts and eliminate secretions (21). SDF imaging data were recorded and analyzed using real-time quality feedback on adequate focus, contrast and stability with GlycoCheck (GlycoCheck BV, Maastricht, The Netherlands), as described previously (22). The GlycoCheck software automatically calculates the perfused boundary region (PBR), which is a previously validated dimension of the permeable part of the endothelial glycocalyx that does allow red blood cell penetration (23, 24). The red blood cell (RBC) filling percentage is calculated an estimate for microvascular perfusion. Recorded videos were also imported for offline analysis in Automated Vascular Analysis (AVA) software 4.1 (MicroVision Medical BV). The software automatically separates outcome parameters for large (mostly venules) or small (mostly capillaries) vessels using a diameter cutoff value of 20 µm. Total vessel density (TVD), perfused vessel density (PVD), valid vessel density (VVD) and De Backer Score were calculated as measures of microvascular vessel density; the percentage of perfused vessels (%PV) was calculated as the number of vessels continuously perfused divided by the total number of vessels of the same type. The heterogeneity index was defined as the difference between maximal and minimal proportions of perfused vessels evaluated at each visualized area divided by the mean value of the areas (25).

Blood flow velocity (BFV) in the right middle cerebral artery (MCA) was measured at an insonation depth of 50–52 mm by transcranial Doppler (TCD) monitoring using a Pioneer TC 4040. When the optimal TCD signal was achieved, a 2-MHz TCD transducer probe was fixed over the temporal window using an adjustable headset (Marc 500, Spencer Technologies, Nicolet Biomedical).

Experimental procedure

Approximately one hour after ICU admission the experimental procedures were initiated. All measurements were performed with patients in supine position at three sequential time points: pre-intervention, during intervention and post-intervention. Before the intervention (T1), FiO_2 was titrated to a level targeting a partial pressure of arterial oxygen (PaO_2) between 67.5 mmHg (9 kPa) and 82.5 mmHg (11 kPa) and a complete set of hemodynamic measurements was performed. The intervention (T2) commenced by increasing the FiO_2 to 90% and after a 15-min wash-in period, all hemodynamic measurements were repeated. Thereafter (T3), the FiO_2 was decreased by targeting baseline PaO_2 levels, and after 15-min wash-out period, the final control measurements were completed. Before, during and after the intervention, arterial blood gas samples were analyzed to determine arterial oxygenation.

Four 12-second inspiratory hold maneuvers were applied using ventilator plateau pressures of 5, 15, 25 and 35 cm H_2O as previously reported (20). Each successive inspiratory hold was performed when the initial hemodynamic steady state was reestablished. When the plateau pressure increases, CVP increases concomitantly, whereas CO and MAP decrease with a short delay, reaching a steady state at 7–10 s after inflation. From these steady state measurements, a venous return curve was constructed by fitting a linear regression line through four values of CVP and CO. The extrapolated value at zero flow is the mean systemic filling pressure (P_{msf}). Similarly, the ventricular output curve was fitted through the values of MAP and CO, where the regression line crosses the zero flow intercept at the critical closing pressure (P_{cc}) (19).

The resistance of the systemic circulation (R_{sys}) was calculated as the ratio of the pressure difference between MAP and mean CVP, and CO. The resistance at the arterial and venous side of the circulation was also separately calculated as resistance for ventricular output $R_{vo} = (MAP - P_{cc})/CO$ and resistance for venous return $R_{vr} = (P_{msf} - CVP)/CO$ (26).

Statistical analysis:

As this was an exploratory physiological intervention study studying multiple hemodynamic parameters we did not specifically rely on sample size calculation for one single outcome.

The intervention (T2, *hyperoxia*) and post-intervention measurements (T3, *normoxia*), were compared to baseline (T1, *normoxia*) measurements, using a paired t-tests or Wilcoxon signed rank test, depending on the underlying distribution.

Multivariate linear mixed models with random effects per patient were used to compare the exposure (T2) with the non-exposure (T1 and T3) measurements, to account for within-subject correlation and were adjusted for age, temperature, the administered dose of propofol and norepinephrine, and the achieved levels of arterial carbon dioxide ($PaCO_2$) and hemoglobin (Hb).

To account for multiple testing, the indicated levels of statistical significance were lowered to 0.01. All statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients were screened for eligibility from September 2014 until September 2015. Four patients were excluded due to severe postoperative hemodynamic or respiratory instability in the ICU. Baseline characteristics of the twenty-two included patients are listed in Table 1. All participating patients were free of surgical complications, fully recovered from anesthesia within 8 h after surgery and were discharged from the ICU on the first postoperative day. During the experimental procedure, all patients received a glucose 2.5% in 0.45% saline solution at 84 ml/h, propofol (range 200-400 mg h^{-1}) and sufentanil (range 5-25 µg h^{-1}). Two patients additionally received norepinephrine (0.02 and 0.04 µg kg^{-1} min^{-1}) at a constant rate in order to keep the blood pressure in a similar range (MAP higher than 65 mmHg) as the other included patients during the experimental procedure. This was accounted for in the multivariate linear mixed model, and excluding these patients did not materially change the magnitude or direction of our univariate findings.

Table 1. Patient characteristics

Characteristics	All patients (n = 22)
Descriptive characteristics	
Age (year)	63 (59–66)
Male/female (n)	17/5
BMI (kg/m^2)	26 (25–29)
Body temperature (°C)	37 (36–37)
APACHE IV	40 (33–61)
SAPS II	28 (24–32)
Surgical characteristics	
Perfusion time (min)	105 (91–121)
Clamp time (min)	73 (63–82)
ICU ventilator settings	
P_{insp} (cm H_2O)	18 (16–19)
V_T (ml)	585 (484–650)
PEEP (cm H_2O)	5 (5–5)
Respiratory rate (breaths min^{-1})	12 (12–14)
ICU medication	
Propofol (mg h^{-1})	250 (200–288)
Sufentanil (µg h^{-1})	10 (6–10)
Norepinephrine (µg kg^{-1} min^{-1})	0 (0–0), range 0–0.04

Data are medians (interquartile range), unless stated otherwise

BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation score; SAPS, Simplified Acute Physiology Score; P_{insp}, inspiratory pressure; V_T, tidal volume; PEEP, positive end-expiratory pressure

Arterial blood gas parameters

Arterial blood gas values at the three different time points are shown in Table 2. PaO_2 levels pre- and post-hyperoxia matched well with the targeted levels. Also, pre- and post-hyperoxia arterial oxygen saturation (SaO_2) was similar. During hyperoxia PaO_2 and SaO_2 were significantly higher.

$PaCO_2$ decreased over time, whereas hemoglobin, hematocrit, glucose and lactate levels did not change.

Hemodynamic parameters

Hemodynamic values at the three different time points are shown in Table 3. After starting the intervention with 90% oxygen supply, R_{sys} increased (P<0.0001), without altering the heart rate. SVV and PPV decreased slightly. CO did not significantly decrease (P=0.08).

During the hyperoxia period P_{msf} and the slope of the venous return curve ($Slope_{vrc}$) increased (Fig. 1). P_{cc} increased, whereas the slope of the left ventricular output curve ($Slope_{voc}$) did not change. R_{sys} and R_{vr} increased because of the higher MAP and P_{msf} at constant CO. R_{vo} did not change because MAP and P_{cc} increased similarly.

We did not find any reduction in cerebral blood flow and only slight shifts in microcirculatory scores were noted. The percentage of perfused vessels decreased during hyperoxia (P=0.01). No changes in vascular density were detected for either large or small vessels.

The results were virtually unchanged when multivariate mixed models were used (Table 3).

DISCUSSION

In this single-center physiological intervention study, we found that a 15-min exposure to hyperoxia affects hemodynamics in ICU patients after CABG. This was translated in several changes in central

Table 2. Variables of arterial blood gas analyses during different time periods

Variable	T1	T2	T3
	Pre	Hyperoxia	Post
FiO_2 (%)	25 (21–30)	90 (90–90)	21 (21–25)
Arterial blood gas analyses[a]			
SaO_2 (%)	94.9 (1.9)	99.0 (0.3)***	95.7 (1.8)
PaO_2 (mmHg)	83.5 (12.2)	390.2 (93.2)***	87.8 (21.5)
$PaCO_2$ (mmHg)	39.8 (8.1)	36.0 (7.9)**	34.5 (8.7)***
Hb (mmol L^{-1})	7.2 (0.8)	7.4 (0.7)	7.4 (0.8)
Ht (L L^{-1})	0.34 (0.04)	0.35 (0.03)	0.35 (0.04)
Glucose (mmol L^{-1})	7.5 (1.6)	7.4 (1.7)	7.7 (1.8)
Lactate (mmol L^{-1})	1.25 (0.38)	1.20 (0.40)	1.25 (0.34)

FiO2,fraction of inspired oxygen; SaO_2, arterial oxygen saturation; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; Hb, hemoglobin; Ht, hematocrit.
Data are means (SD). For FiO_2, medians (interquartile range) are provided.
* P<0.01, ** P<0.001, ***P<0.0001 for paired comparison between indicated outcome and baseline (T1)
[a] Arterial blood gas samples analyzed prior to the start of hemodynamic measurement

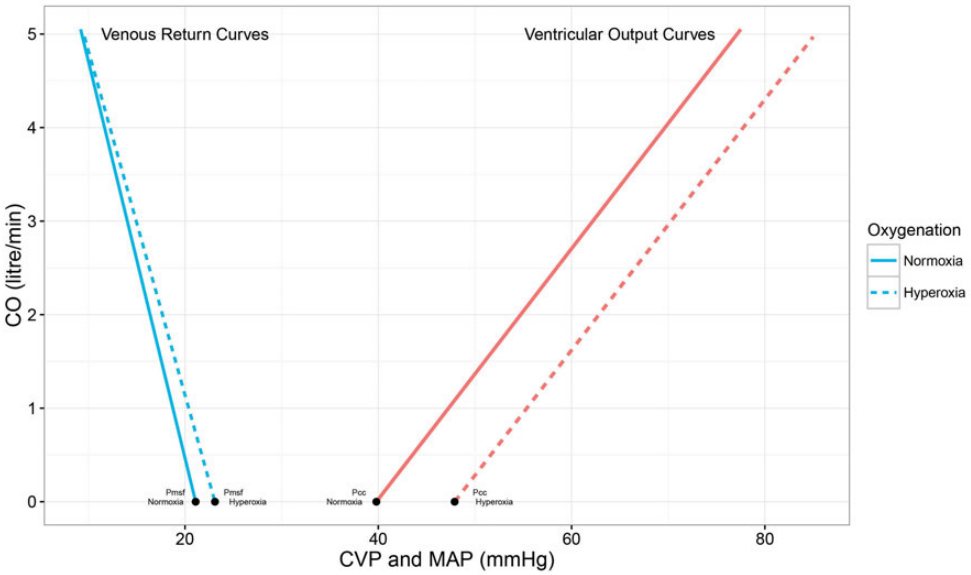

Figure 1. Venous return and ventricular output curves by arterial oxygenation status.
Relationship between cardiac output (CO) and central venous pressure (CVP) in a venous return curve and between CO and mean arterial blood pressure (MAP) in a ventricular output curve for the averaged patient (Table 3). At zero blood flow mean systemic filling pressure (P_{msf}) and critical closing pressure (P_{cc}) are indicated. Venous return curves and ventricular output curves for arterial normoxia (solid line) and hyperoxia (dashed line) are given

circulatory variables and in the percentage of perfused microcirculatory vessels, but showed no alterations in cardiac output and cerebral blood flow.

The circulation of blood can be described by either the CO or the venous return. As only blood returning to the heart can be pumped out in the systemic circulation, venous return should always equal CO. Major determinants of CO are preload, contractility and afterload. During hyperoxia, left ventricular afterload clearly increased. The absence of a measurable decrease in CO may be explained by a concomitant increase in preload. Indeed, we found higher CVP during hyperoxia. The alternative explanation, i.e., increased contractility, is unlikely as we found no increase in the slope of the cardiac output curve during hyperoxia.

The circulation can also be described by the venous return to the heart, which is driven by P_{msf} – CVP. During hyperoxia P_{msf} increased more than CVP. However, this did not lead to an increase of venous return due to the simultaneous increase in venous resistance.

Vasoconstriction may be the key driver of most if not all effects of hyperoxia on hemodynamics. Not only does it increase blood pressure, afterload and venous resistance, it also leads to a shift of blood from unstressed to stressed volume, as indicated by increases in P_{msf} and CVP. We also observed an increase in P_{cc} by hyperoxia. P_{cc} is a theoretical pressure defined by dynamic pressure flow-relations and represents the arterial pressure, below which conceptually no flow will be possible. It is a combined estimate representing all vascular circuits. Theoretically, P_{cc} is the sum

Table 3. Crude hemodynamic measurements during different time periods and adjusted change in estimate with hyperoxic ventilation

Hemodynamic variables	T1 Pre	T2 Hyperoxia	T3 Post	Hyperoxia vs. normoxia Adjusted change in estimate (95% CI)	P-value
Central circulatory variables[a]					
MAP (mmHg)	77 (11)	85 (11)***	78 (11)	6.76 (3.88; 9.63)	<0.0001
CVP (mmHg)	9.1 (1.7)	9.6 (1.7)	9.3 (1.6)	0.35 (0.11; 0.60)	0.01
HR (beats min^{-1})	84 (14)	82 (14)	83 (15)	-0.55 (-3.05; 2.06)	0.68
Calculated variables					
CO *Modelflow* (L min^{-1})[b]	5.12 (1.04)	4.97 (1.13)	4.98 (1.18)	-0.08 (-0.27; 0.11)	0.41
SVV (%)[b]	13.6 (9.3)	13.2 (6.9)	15.3 (7.4)	-1.76 (-3.38; -0.03)	0.05
PPV (%)[b]	15.6 (10.3)	15.1 (7.6)	16.6 (4.9)	-1.30 (-2.99; 0.49)	0.16
CO *LiDCOplus* (L min^{-1})[c]	4.80 (1.10)	4.62 (1.10)	4.79 (1.27)	-0.12 (-0.40; 0.08)	0.21
Derived parameters[d]					
R_{sys} (mmHg min L^{-1})	13.4 (4.9)	15.3 (5.9)***	13.6 (5.1)	1.82 (0.96; 2.67)	<0.001
P_{vr} (mmHg)	11.7 (3.3)	13.5 (3.5)*	12.1 (2.8)	1.47 (0.61; 2.37)	<0.01
R_{vr} (mmHg min L^{-1})	2.4 (0.8)	2.8 (1.0)**	2.5 (0.8)	0.39 (0.21; 0.58)	<0.001
$Slope_{vrc}$ (L min^{-1} $mmHg^{-1}$)	-0.46 (0.16)	-0.38 (0.13)**	-0.44 (0.15)	0.07 (0.03; 0.10)	<0.001
P_{msf} (mmHg)	20.8 (3.5)	23.1 (4.0)*	21.4 (2.9)	1.90 (0.95; 2.93)	<0.001
R_{vo} (mmHg min L^{-1})	7.9 (3.2)	7.9 (4.3)	7.7 (1.9)	-0.09 (-1.17; 1.03)	0.87
$Slope_{voc}$ (L min^{-1} $mmHg^{-1}$)	0.13 (0.05)	0.15 (0.11)	0.14 (0.04)	0.01 (-0.03; 0.05)	0.62
P_{cc} (mmHg)	38.8 (9.8)	47.9 (15.1)*	40.9 (8.9)	8.55 (4.13; 12.68)	<0.001
Cerebral blood flow[e]					
BFV_{mca} (cm s^{-1})	34.6 (10.6)	32.3 (10.3)	33.6 (11.5)	-1.42 (-3.80; 1.01)	0.26
Pulsatility Index	0.95	0.96	1.0	-0.03 (-0.07; 0.01)	0.17
Resistance Index	0.57	0.57	0.58	0 (-0.01; 0.01)	0.66
Microcirculation[f]					
RBC filling (%)	72.3 (4.4)	71.1 (5.0)	72.9 (5.1)	-1.87 (-3.29; -0.34)	0.02
PBR (µm)	2.1 (0.2)	2.2 (0.2)	2.1 (0.2)	0.05 (-0.03; 0.12)	0.21
TVD (mm/mm^2)	12.2 (3.5)	12.7 (3.5)	12.0 (3.4)	0.35 (-0.96; 2.08)	0.66
PVD (mm/mm^2)	12.0 (3.7)	12.1 (2.9)	12.0 (3.1)	-0.03 (-1.50; 1.70)	0.97

Table 3. (continued)

Hemodynamic variables	T1 Pre	T2 Hyperoxia	T3 Post	Hyperoxia vs. normoxia Adjusted change in estimate (95% CI)	P-value
VVD (µm/mm²)	712 (117)	672 (130)	699 (93)	-37.29 (-80.97; 8.01)	0.11
DeBacker score (n/mm)	14.2 (1.2)	15.1 (1.6)	14.4 (1.6)	0.86 (0.23; 1.51)	0.01
PV (%)	99.6 (1.3)	93.2 (8.3)*	97.4 (6.1)	-4.72 (-7.64; -2.00)	<0.01
	100 (IQR 99-100)	98 (IQR 85-100)	100 (IQR 99-100)	–	–
Heterogeneity Index (%)	13 [9–14]	22 [21–23]***	21 [15–21]***	–	–

MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; CO, cardiac output; SVV, stroke volume variation; PPV, pulse pressure variation; R_{sys}, resistance of the systemic circulation; P_{vr}, pressure difference between P_{msf} and P_{cv}; R_{vr}, resistance for venous return; $Slope_{vrc}$, slope of venous return curve; P_{msf}, mean systemic filling pressure; R_{vo}, resistance for ventricular output; $Slope_{voc}$, slope of ventricular output curve; P_{cc} critical closing pressure; BFV_{mca}, blood flow velocity in middle cerebral artery; RBC, red blood cell; PBR, perfused boundary region; TVD, total vascular density; PVD, perfused vascular density; VVD, valid vascular density; PV, perfused vessels.

Data are means (SD). For PV (%), medians (interquartile range) are provided.

* P<0.01, ** P<0.001, ***P<0.0001 for paired comparison between indicated outcome and baseline (T1)

[a] Directly measured from radial artery and central venous catheters

[b] Calculated beat-to-beat by pulse contour analysis from Modelflow and averaged over indicated time period

[c] Calculated by pulse contour analysis from LiDCO*plus* 15-min after starting the exposure at indicated time period

[d] Secondarily derived from Modelflow calculated variables

[e] Directly measured using transcranial Doppler on middle cerebral artery

[f] Calculated from sublingual sidestream dark field imaging analyses

Change in estimate (95% CI) with intervention (hyperoxia) in reference to normoxia periods from linear mixed model adjusted for age, temperature, Hb, $PaCO_2$, norepinephrine dose and propofol dose. P-value calculated using t-tests with Satterthwaite approximations to degrees of freedom

of arterial wall tension and the pressure surrounding the blood vessel. P_{cc} may differ importantly between different vessels, and measured P_{cc} is an average value for the complete vasculature. An increase in P_{cc} may be especially relevant in certain disease states such as increased intracranial pressure and abdominal compartment syndrome with high pressures surrounding the vessels. In both situations, P_{cc} is markedly elevated. For example, intracerebral blood flow will decrease to zero when arterial blood pressure is lower than the critical closing pressure of the brain and beyond the limits of cerebral autoregulation. In such states, vasoconstriction, by either vasoactive drugs or hyperoxia, may have either beneficial effects by increasing blood pressure or harmful effects by increasing arterial wall tone and thereby $P_{cc.}$

In our study, we could not show a reduction in perfusion of the brain by hyperoxia. Similarly, in a previous report perfusion changes at all oxygen levels were relatively small (27, 28). It should be noted that all these studies were performed in situations with normal intracranial pressure. In situations with intracranial hypertension, such as in traumatic brain injury, we cannot rule out that a further increase of P_{cc} by hyperoxia will decrease the pressure difference between P_a and P_{cc} which can lead to a lower perfusion and possible ischemia of the brain.

Comparing our findings with earlier studies on the effects of hyperoxia on hemodynamics, the cardiac output fall was less than in healthy volunteers (29) and the decrease in the percentage of perfused vessels of the microcirculation was also in a different order of magnitude than previously observed (30). Recognizing the perfused boundary region of microcirculatory vessels as a surrogate measure for the dimension of the glycocalyx, we could not detect any hyperoxia-induced alterations. Considering the effects on the venous system, more pronounced effects are to be expected in the smaller vessels compared to larger vessels. As a limited number of arterioles are present in the sublingual mucosa, where capillaries and venules are more abundant, only slight changes were anticipated in the analyzed microcirculation when high oxygen levels are applied.

Study differences may be largely explained by the use of anesthesia and mechanical ventilation as both affect hemodynamics and anesthesia also induces a considerable decrease in stressed volume. Furthermore, even in the presence of healthy lungs, both mechanical ventilation and bypass surgery may inflict an inflammatory response which can modify the effects of hyperoxic ventilation on the circulation in comparison with healthy subjects. Remaining differences may be clarified by the short exposure time in our procedures, although no further increase in PaO_2 was to be expected from a longer exposure and therefore a steady state in hemodynamics was assumed.

The increase in stressed volume and P_{msf} by hyperoxia mimics the effects of administering a fluid bolus, yet without increasing the R_{vr}. It is well known that the effects of extra fluids on CO are most pronounced in situations with underfilling of the vasculature explaining the relative conservation of cardiac output during hyperoxia in our postoperative, sedated patients, compared to healthy subjects. The effects of hyperoxia closely resemble the effects of norepinephrine and are in contrast to the effects of propofol (31, 32). We earlier showed that intravenous administration of norepinephrine resulted in increases in R_{sys}, R_{vr} and P_{msf}. Interestingly, CO increased in some but not all patients after norepinephrine (32). An increase in CO was associated with a higher SVV. Thus, it appears likely that the effects of a shift from unstressed to stressed volume by vasoconstriction, with an increase in P_{msf}, is mostly found in patients with vasoplegia and/or a decreased circulating

volume. Hence, the effects of hyperoxia on CO are determined by the balance between volume recruitment (P_{msf}) and change in R_{vr} and baseline heart function, as observed before (32). Although our results clearly indicate that hyperoxia increases venous resistance by venous vasoconstriction and that left ventricular output resistance (R_{vo}) did not change, we must realize that our description of the circulation is not complete. We cannot describe the part between the site where P_{cc} exists and the site where P_{msf} exists. Therefore, there is a missing part of the circulatory circuit, i.e., the distal arterial compartment, where control of the peripheral circulation is performed by the pre-capillary sphincters.

A recent study with an alternative cardiac output monitor of the arterial pressure wave showed a poor correlation with the thermodilution obtained CO values while changing norepinephrine doses (33). However, measurements carried out by our group suggest that the Modelflow technique is capable of measuring the effects induced by vasoconstriction in an accurate manner (32), suggesting that vasoactive agents may not importantly affect the precision of your technology. This was also underlined by the CO values measured by the LiDCO*plus* monitor that showed a similar pattern compared to the Modelflow technique in our study. Furthermore, the determination of P_{msf} is not dependent on the accuracy of the Modelflow technique. Indeed, extrapolation of the venous return curve to flow zero is independent of absolute cardiac output. The ability to follow changes in cardiac output within a patient has been clearly demonstrated before (18). We also showed that beat-to-beat changes in Modelflow cardiac output follows cardiac output by beat-to-beat analysis of electromagnetic probe flow signals (19).

Acknowledging that our findings are to be reproduced in a larger cohort and different clinical settings, the following study aspects should be considered. First, the small sample size and the specific subgroup of patients do not warrant a broad generalizability for the observed effects. Hemodynamics in the current patient group may be affected by the effects of the recent bypass and the potential mediators of ischemia reperfusion and inflammation. Other subsets of critically ill patients may respond differently than patients in our cohort who were in a relatively stable condition before starting study procedures. Two patients received small doses of norepinephrine during the experiment to keep the blood pressure in the same order of magnitude as the other included patients but showed stable hemodynamics and the dose was not changed throughout the experiment. Also, excluding these patients from our analyses showed virtually no change in our results.

There may be a time effect in which recovery and stabilization of patients in the ICU after surgery may influence hemodynamics. However, assuming that the effect of hyperoxia was transient and respecting a 15-min time gap between the two exposures, the carryover effect was minimized and each case served as its own control (self-matched) (34). Adjusted changes in estimates were based on within-subject comparisons of exposure to hyperoxia with exposure to normoxia. Sampling bias was minimized by continuously measuring central circulatory variables, which provide a highly accurate representation of the parameters over the time periods. Cerebral blood flow, microcirculation and parameters assessed from the inspiratory hold procedures were measured intermittently, yet at representative sampling moments during the sequential time points and averaged as appropriate.

Since we could not detect large differences between the outcomes of univariate and multivariate statistical models accounting for repeated measurements, the observed effects may be predominantly attributed to hyperoxic ventilation, rather than to concomitant changes in other parameters. Other covariates that were considered, such as $PaCO_2$, are therefore not a likely explanation for the hemodynamic changes as seen during the experiment. While a short period of supraphysiological arterial oxygenation may disturb the hemodynamic balance, the effects of long-term exposure to hyperoxia are still uncertain but may be essential regarding patient-centered outcomes.

CONCLUSIONS

Short-term hyperoxia after cardiac surgery induces significant alterations in systemic circulation mainly by vasoconstriction of both the venous and arterial circulation and an increase of mean systemic filling pressure. The increase in stressed volume and systemic filling pressure by hyperoxia resembles the effects of administering a fluid bolus or norepinephrine. This may have clinically important consequences in critically ill patients when hemodynamic and microcirculatory changes are vital, but the effects were not clearly linked to relevant changes in cardiac output and cerebral blood flow.

LIST OF ABBREVIATIONS

APACHE, Acute Physiology and Chronic Health Evaluation score; APRV, airway pressure release ventilation; AVA, Automated Vascular Analysis; BFV, blood flow velocity; CABG, coronary artery bypass grafting; CO, cardiac output; CVP, central venous pressure; ICU, intensive care unit; FiO_2, fraction of inspired oxygen; Hb, hemoglobin; Ht, hematocrit; HR, heart rate; MAP, mean arterial pressure; MCA, middle cerebral artery; NTR, Netherlands Trial Register; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; PBR, perfused boundary region; P_{cc}, critical closing pressure; PEEP, positive end-expiratory pressure; P_{insp}, inspiratory pressure; P_{msf}, mean systemic filling pressure; PPV, pulse pressure variation; PV, perfused vessels; PVD, perfused vessel density; RBC, red blood cell; R_{sys}, resistance of the systemic circulation; R_{vo}, resistance for ventricular output; R_{vr}, resistance for venous return; SaO_2, arterial oxygen saturation; SAPS, Simplified Acute Physiology Score; SDF, sidestream dark field; $Slope_{voc}$, slope of ventricular output curve; $Slope_{vrc}$, slope of venous return curve; SVV, stroke volume variation; TCD, transcranial Doppler; TVD, total vessel density; V_T, tidal volume; VVD, valid vessel density.

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5

ASSOCIATIONS OF ARTERIAL CARBON DIOXIDE AND ARTERIAL OXYGEN CONCENTRATIONS WITH HOSPITAL MORTALITY AFTER RESUSCITATION FROM CARDIAC ARREST

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ABSTRACT

Introduction

Arterial concentrations of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) during admission to the intensive care unit (ICU) may substantially affect organ perfusion and outcome after cardiac arrest. Our aim was to investigate the independent and synergistic effects of both parameters on hospital mortality.

Methods

This was a cohort study using data from mechanically ventilated cardiac arrest patients in the Dutch National Intensive Care Evaluation (NICE) registry between 2007 and 2012. $PaCO_2$ and PaO_2 levels from arterial blood gas analyses corresponding to the worst oxygenation in the first 24 h of ICU stay were retrieved for analyses. Logistic regression analyses were performed to assess the relationship between hospital mortality and both categorized groups and a spline-based transformation of the continuous values of $PaCO_2$ and PaO_2.

Results

In total, 5,258 cardiac arrest patients admitted to 82 ICUs in the Netherlands were included. In the first 24 h of ICU admission, hypocapnia was encountered in 22%, and hypercapnia in 35% of included cases. Hypoxia and hyperoxia were observed in 8% and 3% of the patients, respectively. Both $PaCO_2$ and PaO_2 had an independent U-shaped relationship with hospital mortality and after adjustment for confounders, hypocapnia and hypoxia were significant predictors of hospital mortality: OR 1.37 (95% CI 1.17–1.61) and OR 1.34 (95% CI 1.08–1.66). A synergistic effect of concurrent derangements of $PaCO_2$ and PaO_2 was not observed (P = 0.75).

Conclusions

The effects of aberrant arterial carbon dioxide and arterial oxygen concentrations were independently but not synergistically associated with hospital mortality after cardiac arrest.

INTRODUCTION

Even after successful resuscitation and return of spontaneous circulation (ROSC), cardiac arrest carries a poor prognosis with limited options for treatment (1, 2). In addition to controlling temperature after cardiac arrest, optimizing ventilation and oxygenation may improve outcome (3). International consensus currently recommends careful monitoring of post-resuscitation ventilation for neurological and cardiovascular outcome (4). Indeed, targeting safe levels of carbon dioxide and oxygen in arterial blood may limit global ischemic damage and enhance oxygenation and blood flow. Aberrant arterial levels have repeatedly been shown to be associated with worse outcome after cardiac arrest, but the effects may depend on degree and duration of the (concurrent) exposure (5-14). Recently, a large cohort study was performed in 125 intensive care units (ICUs) in Australia and New Zealand, which showed that abnormal concentrations of arterial carbon dioxide ($PaCO_2$) were common after cardiac arrest (15). Compared with normocapnia, hypocapnia was independently associated with worse clinical outcomes, whereas hypercapnia was associated with a greater likelihood of good outcome. The results were reproduced in a smaller cohort (16) and are supported by pediatric (17) and experimental research (18-20). However, ventilation and oxygenation are closely related and effects of $PaCO_2$ may not be independent from arterial oxygen levels (PaO_2). In this study, we aimed to investigate the separate and combined effects of both parameters in a multicenter cohort of patients admitted to Dutch ICUs after cardiac arrest.

METHODS

Data collection

Analyses were performed on patient data retrieved from 82 ICUs of teaching and non-teaching hospitals participating in the Dutch National Intensive Care Evaluation (NICE) registry between 2007 and 2012. The NICE registry is a high quality ICU database, which is subject to multiple quality checks and local audits in accordance with applicable research and ethical protocols (21). In brief, the registry contains all clinical data required to calculate mortality risk predictions according to, among others, the Acute Physiology and Chronic Health Evaluation (APACHE) IV for all consecutive ICU patients. The registry does not contain variables determining the cause and circumstances of the cardiac arrest and resuscitation. For the analyses, data obtained from routine care and without patient identifying information was used and consent was therefore not needed according to the Dutch Personal Data Protection Act.

In 2012, approximately 90% of all Dutch ICUs recorded the data for their patients in the registry. In accordance with the previously conducted study by Schneider et al. (15), all adult patients admitted after out-of-hospital cardiac arrest were included. Abstracted data included demographics, comorbidities, arterial blood gas parameters, diagnostic and physiologic information, admission source and illness severity score by means of the APACHE IV.

Data extraction

Adult patients admitted to the ICU after out-of-hospital cardiac arrest and cardiopulmonary resuscitation, whom were mechanically ventilated at any moment in the first 24 hours of admission,

were included. We excluded readmissions, trauma patients, nonventilated patients and records not meeting APACHE IV criteria.

As part of the NICE data collection, arterial blood gas (ABG) parameters that were associated with the lowest PaO_2 to FiO_2 ratio in the first 24h after admission were automatically extracted and subsequently used for classification of patients. The APACHE IV score was recalculated (AP4-adj) by standardizing the $PaCO_2$ and PaO_2 to fixed normal values (40 mmHg and 80 mmHg, respectively) in order to prevent overadjustment of these variables in the multivariate models.

Statistical analysis

Univariate and multivariate logistic generalized estimating equation (GEE) regression models, which account for potential correlation of outcome within ICUs, were used to examine the relationship between the primary outcome (hospital mortality) and either $PaCO_2$ or PaO_2. The relationship of $PaCO_2$ and PaO_2 with mortality were plotted in order to inspect the dose-response curve. Considering the nonlinear relationships, the associations were analyzed by modeling each of $PaCO_2$ and PaO_2 as a restricted cubic spline and separately in categorized groups (22). $PaCO_2$ was categorized in three groups, using conventional thresholds (normocapnia: 35-45 mmHg). PaO_2 was categorized according to thresholds from previous studies (normoxia: 60-300 mmHg) (5, 7-9, 23, 24). The individual, joint and interaction effects of two-sided derangements were separately investigated, as suggested for cohort studies (25). For a further understanding of the dose-response relationship in multivariate models, PaO_2 categories were also reanalysed with alternative thresholds derived from observation percentiles or previously used targets (5, 7, 8, 26). Variables extracted from the first 24 hours of admission were considered for the multivariate etiological model based on clinical relevance and in accordance with a previously used model (15). Considered covariates were introduced separately to the univariate models in order to estimate the unadjusted effect and included age, gender, AP4-adj, year of admission, admission source, therapeutic hypothermia and lowest glucose as a possible proxy-marker of less attentive care (24). Covariates were subsequently identified as confounders for the outcome using the 10% change-in-estimate method (27). Hence, the final multivariate GEE models consisted of age, lowest glucose, AP4-adj and either $PaCO_2$ or PaO_2. Collinearity among the covariates was inspected by estimating Pearson or Spearman correlation coefficients as appropriate. Routine temperature correction of arterial blood gas results is uncommon in Dutch ICUs and was performed according to the participating site's practice. To account for multiple testing, the statistical significance level for the P-value was set at 0.01.

All analyses were conducted using SPSS version 21 (IBM Corp, Armonk, NY, USA) and R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Data from 6,496 out-of-hospital cardiac arrest patients and 82 hospitals were extracted from the NICE registry and screened for enrollment (Supplemental figure 1). The main reasons for exclusion were no mechanical ventilation (n=196), missing valid ABG data (n=379) and not fulfilling APACHE IV criteria (n=314).

Descriptive characteristics of the 5,258 included patients are summarized in Table 1. The median age was 66 (IQR 56-76) and patients were predominantly male (69.6%). Median $PaCO_2$ was 42 mmHg (IQR 36-49) and median PaO_2 was 92 mmHg (IQR 75-124). Of all patients, 21.6% were classified as hypocapnic, 43.5% as normocapnic and 34.9% as hypercapnic. Patients were further classified as hypoxic (8%), normoxic (89.3%) or hyperoxic (2.7%). The majority of patients (87.4%) were admitted to the ICU from the emergency room of the same hospital. The unadjusted mean APACHE IV score was 117.3, with the normocapnia and the normoxia groups showing the lowest mean (P<0.001). Groups were relatively balanced in terms of admission source, comorbidities, temperature, glucose and non-respiratory markers.

Unadjusted outcome

Table 2 shows the unadjusted mortality rates. Overall, 2,491 (47.4%) patients died in the ICU and 2,833 (53.9%) died in the hospital. Hospital mortality was highest in the hypocapnia group (58.4%), compared with the hypercapnia (56.8%) and normocapnia (49.3%) group (P<0.001). Compared with the hyperoxia (57.6%) and normoxia (52.9%) groups, hospital mortality was higher (P<0.001) in the hypoxia group (63.6%).

In the univariate logistic regression model, $PaCO_2$ was significantly associated with mortality (P<0.001). This model was improved when PaO_2 was added (P<0.001). No interaction effect (arterial oxygen by arterial carbon dioxide concentration) on mortality was found (P=0.25). PaO_2 was also univariately associated with hospital mortality (P<0.001).

Adjusted outcomes

Both $PaCO_2$ and PaO_2 showed a curvilinear U-shaped relationship with mortality in adjusted analyses (Fig. 1 and 2).

Odds ratios from multivariate analyses are listed in Table 3. After adjustment for age, lowest glucose, AP4-adj and PaO_2 (splines), hypocapnia showed a significant association with hospital mortality (P<0.001), whereas hypercapnia did not. When this model was reanalyzed without adjustment for PaO_2, the results were virtually unchanged (data not shown).

Adjusted for age, lowest glucose, AP4-adj and $PaCO_2$ (splines), hypoxia but not hyperoxia was found to be associated with hospital mortality in comparison to normoxia (P<0.01). When this model was reanalyzed without adjustment for $PaCO_2$ the results were not materially different (data not shown). When the model was reanalyzed with hyperoxia (>300 mmHg) as reference category, no effects on mortality were observed for various oxygenation ranges.

The individual and joint effect estimates for derangements (normal range vs. outside normal range) of both parameters are listed in Table 4. Aberrant levels of both $PaCO_2$ and PaO_2 were independently associated with hospital mortality (P<0.01). The estimate for the interaction term (presence of $PaCO_2$ derangement by presence of PaO_2 derangement) was not significant on a multiplicative scale (P=0.75).

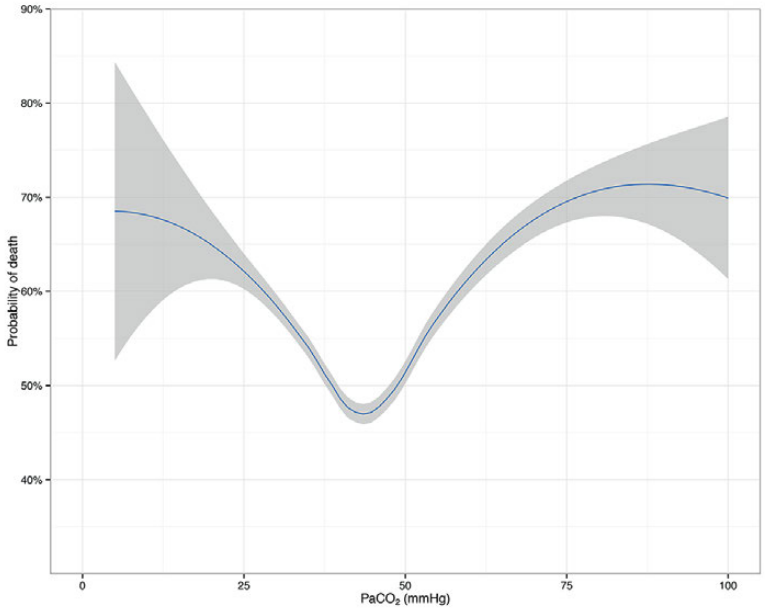

Figure 1. Adjusted probability of in-hospital death by arterial carbon dioxide levels.
Loess smoothing curve predicted from logistic regression model adjusted for spline functions of age, lowest glucose, AP4-adj and PaO_2. Grey zones represent 95% confidence intervals

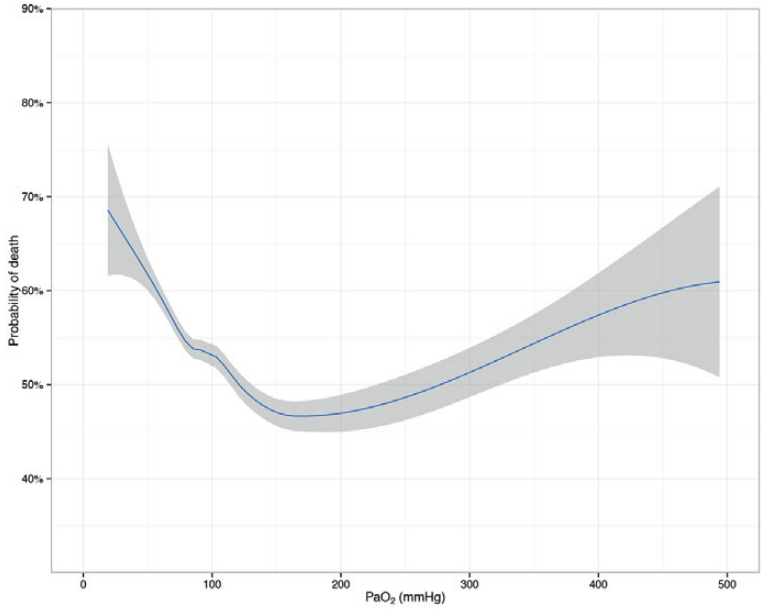

Figure 2. Adjusted probability of in-hospital death by arterial oxygen levels.
Loess smoothing curve predicted from logistic regression model adjusted for spline functions of age, lowest glucose, AP4-adj and $PaCO_2$. Grey zones represent 95% confidence intervals

Table 1. Descriptive characteristics

Characteristic	All patients	$PaCO_2$ group				PaO_2 group			
		Hypocapnia	Normocapnia	Hypercapnia	*P* value	Hypoxia	Normoxia	Hyperoxia	*P* value
No. (%) of patients	5258	1136 (21.6)	2288 (43.5)	1834 (34.9)		418 (8.0)	4696 (89.3)	144 (2.7)	
Baseline characteristics									
Age (years)	66 (56-76)	68 (56-77)	66 (56-76)	65 (55-74)	<0.001	69 (57-78)	66 (56-75)	67 (56-77)	0.02
Male gender, n (%)	3661 (69.6)	737 (64.9)	1601 (70.0)	1323 (72.1)	<0.001	294 (70.3)	3269 (69.6)	98 (68.1)	0.87
Admission source, n (%)									
Operating room from emergency room same hospital	182 (3.5)	32 (2.8)	95 (4.2)	55 (3.0)	0.05	14 (3.3)	166 (3.5)	2 (1.4)	0.38
Emergency room same hospital	4578 (87.1)	981 (86.4)	1972 (86.2)	1625 (88.6)	0.05	367 (87.8)	4077 (86.8)	134 (93.1)	0.08
Operating room from emergency room other hospital	4 (0.1)	1 (0.1)	1 (<0.1)	2 (0.1)	0.74	0	4 (0.1)	0	0.79
Emergency room other hospital	183 (3.5)	41 (3.6)	81 (3.5)	61 (3.3)	0.90	16 (3.8)	166 (3.5)	1 (0.7)	0.17
Home	311 (5.9)	81 (7.1)	139 (6.1)	91 (5.0)	0.05	21 (5.0)	283 (6.0)	7 (4.9)	0.61
Chronic co-morbidities, n (%)									
Acute renal failure, n (%)	660 (12.6)	154 (13.6)	242 (10.6)	264 (14.4)	<0.001	79 (18.9)	565 (12.0)	16 (11.1)	<0.001
Cardiovascular disease	380 (7.2)	94 (8.3)	158 (6.9)	128 (7.0)	0.30	30 (7.2)	340 (7.2)	10 (6.9)	0.99
Renal disease	319 (6.1)	87 (7.7)	137 (6.0)	95 (5.2)	0.04	24 (5.7)	287 (6.1)	8 (5.6)	0.91
Respiratory disease	225 (4.3)	33 (2.9)	72 (3.1)	120 (6.5)	<0.001	26 (6.2)	191 (4.1)	8 (5.6)	0.08
Cirrhosis	44 (0.8)	16 (1.4)	14 (0.6)	14 (0.8)	0.05	9 (2.2)	35 (0.7)	0	<0.01
Cancer	106 (2.0)	25 (2.2)	48 (2.1)	33 (1.8)	0.62	6 (1.4)	96 (2.0)	4 (2.8)	0.57
Markers of severity,									
APACHE IV score	117.3 (29.69)	117.5 (29.10)	114.6 (30.52)	120.4 (28.68)	<0.001	132.2 (29.22)	115.9 (29.47)	119.5 (26.21)	<0.001
APACHE IV risk of death	80.7 (65.3-90.0)	81.2 (66.2-90.2)	79.2 (63.0-89.2)	82.5 (68.2-91.1)	<0.001	88.8 (78.1-94.0)	79.8 (64.3-89.4)	81.9 (64.9-89.4)	<0.001

Table 1. (continued)

Characteristic	All patients	$PaCO_2$ group				PaO_2 group			
		Hypocapnia	Normocapnia	Hypercapnia	*P* value	Hypoxia	Normoxia	Hyperoxia	*P* value
Physiological parameters obtained within the first 24 h in the intensive care unit									
Temperature									
Highest temperature (°C)	35.7 (34.8-36.9)	35.8 (34.7-37.0)	35.7 (34.8-36.8)	35.8 (34.8-36.9)	0.37	35.7 (34.6-37.1)	35.7 (34.8-36.9)	35.9 (34.9-36.8)	0.88
Lowest temperature (°C)	32.5 (31.8-33.2)	32.4 (31.8-33.4)	32.5 (31.9-33.2)	32.5 (31.9-33.3)	0.55	32.5 (31.8-33.6)	32.5 (31.8-33.2)	32.4 (31.7-33.3)	0.78
Lowest temperature below 34°C, n (%)	4229 (80.4)	888 (78.2)	1863 (81.4)	1478 (80.6)	0.08	326 (78.0)	3788 (80.7)	115 (79.9)	0.41
Heart Rate									
Highest heart rate, beats/min	103 (87-120)	102 (85-120)	101 (86-119)	105 (90-122)	<0.001	110 (91-128)	102 (87-120)	105 (88-125)	<0.001
Lowest heart rate, beats/min	55 (45-68)	55 (45-69)	53 (44-65)	55 (45-70)	<0.001	55 (45-74)	55 (45-67)	51 (42-67)	0.11
Blood pressure (BP)									
Highest systolic BP (mmHg)	150 (134-171)	150 (134-170)	150 (134-172)	150 (133-170)	0.61	145 (128-165)	150 (134-172)	156 (139-178)	<0.001
Lowest systolic BP (mmHg)	80 (70-90)	80 (71-91)	81 (70-90)	80 (69-89)	<0.001	76 (64-86)	80 (70-90)	82 (70-91)	<0.001
Respiratory rate (RR)									
Highest RR, breaths (min)	23 (20-28)	23 (19-29)	23 (19-28)	24 (20-29)	<0.001	25 (20-30)	23 (20-28)	23 (19-28)	<0.01
Lowest RR, breaths (min)	14 (12-16)	14 (12-16)	14 (11-16)	14 (12-17)	0.03	15 (12-18)	14 (12-16)	14 (12-16)	<0.001
Oxygenation									
PaO_2 (mmHg)	92 (75-124)	99 (78-136)	94 (76-125)	87 (70-116)	<0.001	51 (44-56)	94 (78-124)	359 (320-438)	<0.001
FiO_2 (%)	50 (40-70)	45 (40-60)	50 (40-62)	60 (44-90)	<0.001	66 (50-100)	50 (40-70)	98 (67-100)	<0.001
PaO_2/FiO_2 ratio	191 (124-272)	227 (157-316)	203 (134-283)	158 (100-228)	<0.001	71 (55-100)	198 (136-272)	440 (361-550)	<0.001

Table 1. (continued)

Characteristic	All patients	$PaCO_2$ group				PaO_2 group			
		Hypocapnia	Normocapnia	Hypercapnia	*P* value	Hypoxia	Normoxia	Hyperoxia	*P* value
Carbon dioxide									
$PaCO_2$ (mmHg)	42 (36-49)	31 (28-33)	40 (38-43)	52 (48-59)	<0.001	45 (38-54)	41 (35-48)	40 (34-48)	<0.001
Metabolic									
Lowest glucose (mmol l^{-1})	6.0 (4.8-7.4)	5.9 (4.8-7.3)	6.0 (4.8-7.3)	6.1 (4.8-7.5)	0.65	6.2 (4.8-7.9)	6.0 (4.8-7.3)	6.1 (5.0-7.8)	0.13
Acid-base balance									
Lowest pH	7.28 (0.12)	7.37 (0.11)	7.30 (0.10)	7.20 (0.12)	<0.001	7.24 (0.14)	7.29 (0.12)	7.26 (0.14)	<0.001
Highest HCO_3 - (mmol l^{-1})	22.3 (3.92)	20.8 (3.67)	22.1 (3.54)	23.5 (4.16)	<0.001	22.8 (4.70)	22.3 (3.85)	22.0 (3.89)	0.43
Lowest HCO_3 - (mmol l^{-1})	17.4 (4.33)	16.0 (4.17)	17.4 (4.03)	18.3 (4.54)	<0.001	16.6 (4.96)	17.5 (4.27)	17.2 (4.10)	<0.01

Data presented as total number (percentage), mean (standard deviation) or median (interquartile range) depending on underlying data distribution
P-values for group comparisons using ANOVA or Kruskal-Wallis according to data distribution

Table 2. Unadjusted mortality rates

		$PaCO_2$ group				PaO_2 group			
Outcome	**All patients**	**Hypocapnia**	**Normocapnia**	**Hypercapnia**	***P* value**	**Hypoxia**	**Normoxia**	**Hyperoxia**	***P* value**
Intensive care unit mortality	2491 (47.4)	576 (50.7)	976 (42.7)	939 (51.2)	<0.001	244 (58.4)	2171 (46.2)	76 (52.8)	<0.001
In-hospital mortality	2833 (53.9)	663 (58.4)	1129 (49.3)	1041 (56.8)	<0.001	266 (63.6)	2484 (52.9)	83 (57.6)	<0.001

Data presented as total number (percentage) per group. *P*-values for group comparisons using Chi-squared test

Table 3. Adjusted associations between subgroups and hospital mortality

Group comparison	Odds ratio (95% CI)	*P* value
$PaCO_2$ groups		
Hypocapnia vs. normocapnia	1.39 (1.18–1.63)[a]	<0.001
Hypercapnia vs. normocapnia	1.10 (0.95–1.27)[a]	0.20
Hypercapnia vs. hypocapnia	0.79 (0.67–0.94)[a]	<0.01
PaO_2 groups		
Hypoxia vs. normoxia	1.34 (1.08–1.66)[b]	<0.01
Hyperoxia vs. normoxia	1.13 (0.81–1.57)[b]	0.46
Hyperoxia vs. hypoxia	0.85 (0.58–1.24)[b]	0.39
Alternative PaO_2 categories[c]		
55-80 vs. >300 mmHg	1.06 (0.76–1.50)[b]	0.72
80-102 vs. >300 mmHg	0.90 (0.64–1.27)[b]	0.55
102-300 vs. >300 mmHg	0.79 (0.56–1.11)[b]	0.17

Hypocapnia = $PaCO_2$ <35 mmHg; normocapnia = $PaCO_2$ 35-45 mmHg; hypercapnia = $PaCO_2$ >45 mmHg
Hypoxia = PaO_2 <60 mmHg; normoxia = PaO_2 60-300 mmHg; hyperoxia = PaO_2 >300 mmHg
[a] Multivariable analysis adjusted for age, lowest glucose, AP4-adj and PaO_2 (splines)
[b] Multivariable analysis adjusted for age, lowest glucose, AP4-adj and $PaCO_2$ (splines)
[c] Stratification based on thresholds from ARDSnet oxygenation target (55-80 mmHg), upper threshold of median cohort quintile (102 mmHg), and threshold from previous studies (300 mmHg)

Table 4. Associations between derangements and hospital mortality

Variable	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	*P* value
$PaCO_2$ derangement vs. normocapnia	1.38 (1.24–1.54)	1.21 (1.07–1.36)[a]	0.003
PaO_2 derangement vs. normoxia	1.45 (1.21–1.74)	1.27 (1.05–1.54)[b]	0.01
Interaction term	-	1.07 (0.71–1.62)	0.75

$PaCO_2$ derangement = $PaCO_2$ <35 or $PaCO_2$ >45 mmHg; normocapnia = $PaCO_2$ 35-45 mmHg
PaO_2 derangement = PaO_2 <60 or PaO_2 >300 mmHg; normoxia = PaO_2 60-300 mmHg
[a] Multivariable analysis adjusted for age, lowest glucose, AP4-adj and PaO_2 (splines)
[b] Multivariable analysis adjusted for age, lowest glucose, AP4-adj and $PaCO_2$ (splines)

DISCUSSION

In accordance with previous studies, we found that early exposure to both hypo- and hypercapnia is common in ICU patients resuscitated from cardiac arrest (15, 16). In contrast, hypoxia and severe hyperoxia are uncommon findings early in the ICU stay of Dutch hospitals. Both $PaCO_2$ and PaO_2 had a U-shaped relationship with outcome and after adjustment for known confounders, hypocapnia and hypoxia were significantly associated with hospital mortality. Hyperoxia was not independently associated with higher mortality in comparison with various ranges for normoxia. However, this study may lack power to detect significant associations for severe arterial oxygen derangements considering the low prevalence in the present cohort.

Our adjusted mortality plots and the categorized results stress the importance of aberrant arterial levels after cardiac arrest, but rigid cut-offs for optimal ranges remain to be determined and

validated. Increasing mortality rates may be skewed towards extreme PaO_2 levels in the early phase after cardiac arrest. In line, $PaCO_2$ levels between 40 and 45 mmHg appear to be favorable shortly after ICU admission. The complex U-shape of the survival curves for both parameters may explain the heterogeneity in previously observed associations (14). It shows that unfavorable effects cannot be consistently captured when the results are stratified by groups based on arbitrary thresholds. Indeed, studies assessing arterial hyperoxia with lower thresholds usually failed to show significant effects on outcome, whereas higher risks were observed with substantially higher upper limits (5-9). The current findings validate the recent calls for caution with hyperoxia in cardiac arrest patients only to a limited extent. The prevalence in this cohort shows that hypoxia and hyperoxia are not a common concern shortly after cardiac arrest patients are admitted to Dutch ICUs. In the analyses of those conditions, the relatively small number of exposed patients increases the probability of type 2 errors. Associations are therefore more likely to be consistent with increasing statistical power in the studied subgroups. Moreover, reanalyzing the adjusted effects of oxygenation based on quintiles did not detect a significant association with mortality (data not shown). Hypothesizing that physicians would avoid hypoxia most attentively in the most critically ill patients, hyperoxia could be an indirect marker of illness severity or responsive care, and could thereby reflect worse outcome. Accordingly, hypoxia and hypocapnia may also be markers of less attentive care or prehospital injury.

The absence of a significant interaction effect between $PaCO_2$ and PaO_2 suggests that it is mainly the effect of the individual variables that influences mortality in our model than the absolute effect by the interaction between the two variables. The effect of PaO_2 on hospital mortality is therefore not likely to differ significantly across strata of $PaCO_2$, or vice versa. Further, the effect size did not significantly depend on the concurrent presence of aberrant arterial carbon dioxide and arterial oxygen levels. Conditions, in which both parameters are concurrently and strongly modified may therefore not synergistically increase the risk. However, the univariate associations of $PaCO_2$ and PaO_2 were subtly altered when adjusted for each other and both parameters should therefore judiciously be considered as possible confounders.

For our analyses, we were restricted to the variables that were collected as part of the NICE registry. Our database does not contain prehospital variables, nor does it include all ABG samples per admission, but only a single measurement associated with the worst oxygenation in the first 24 hours. Although this method has not previously been shown to be inferior, the selected data may not be the most representative data over the total ICU stay and may therefore misclassify patients. In addition, selecting either the first, worst or highest value from arterial blood gas sampling emerges as an essential methodological issue for the intended analyses (28). The first measured sample may reflect pre-ICU treatment, including oxygen administration in the ambulance and emergency department. Early oxygen administration can influence oxidative metabolism, respiratory markers, vasoconstrictive status and blood flow (29-31), and may thus be an important predictor of outcome. In fact, both highest and lowest systolic blood pressures were significantly higher in the hyperoxia groups. Further, hyperoxia frequently coincides with hyperventilation and concurrent hypocapnia (32). Interestingly, systemic blood pressures were very similar across the $PaCO_2$ subgroups in this cohort. $PaCO_2$ could yet be an important mediator in vascular effects, cardiopulmonary resuscitation

and cerebral perfusion (13, 33). In view of that, the association between hypocapnia and mortality may be explained by cerebral vasoconstriction, whereas hypercapnia may be less harmful due to increased peripheral tissue oxygenation (34-38).

Although our findings are observational and do not necessarily imply causality, the present results are supported by previous results (5, 15). Our findings regarding hyperoxia are in line with several recent studies (8, 23, 39), even though conflicting results have been documented (6, 7, 24, 40). Parts of the heterogeneity in previous findings may be attributed to the adjustment for $PaCO_2$. Pure oxygen therapy after cardiac arrest has previously been shown to worsen neurological outcome in animal models (41) and exposure to hypocapnia and hypercapnia after ROSC has been associated with poor neurological function at hospital discharge (16). However, the effects of PaO_2 targets on neurological recovery of critically ill patients are still uncertain.

In contrast to the previous study by Schneider et al. (15), both the unadjusted and adjusted association between mortality and hypocapnia were statistically significant. Specific study differences may be explained by population and methodological differences. Our multivariate model differed slightly and there was less dispersion of the carbon dioxide concentrations in our data. Other notable differences between both studies include the substantially lower median PaO_2 (92 vs. 106 mmHg), mean FiO_2 (58 vs. 71%), and marginally lower mean $PaCO_2$ (44 vs. 46 mmHg). Furthermore, the vast majority of patients in our cohort (80 vs. 40%) reached a temperature lower than 34°C during the first 24 hours of ICU admission. Under these conditions, $PaCO_2$ and PaO_2 progressively decrease with decreasing body temperature and the occurrence of hypocapnia and hypoxia may be underestimated with uncorrected ABG levels. However, temperature correction of ABG measurements is ambiguous and was not routinely performed in our study, or in the study by Schneider et al.

In order to consistently assess the relationship between risk factors and outcome, it is important to re-evaluate previously established associations in different populations using robust methodology. The modified methodology of the present study provides further insights in the independent and combined effects of $PaCO_2$ and PaO_2 and accounts for clustering by hospital, interaction effects and model variances. Still, residual confounding by prehospital and Utstein variables cannot be ruled out, and derangements may not be isolated risk factors for mortality.

CONCLUSIONS

In this multicenter cohort study, we have studied the survival probability inferred from different levels of $PaCO_2$ and PaO_2 in post cardiac arrest patients. Most effects were attenuated after adjustment for identified confounders, but hypocapnia and hypoxia were independently associated with hospital mortality. The close relationship between both parameters argues for a concurrent assessment of the effects and further evaluation of target ranges is warranted.

COMPETING INTERESTS

Nicolette F. de Keizer and Marie-José Roos-Blom are employed by the National Intensive Care Evaluation (NICE) foundation. All other authors declare that they have no competing interests.

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6

ASSOCIATION BETWEEN ARTERIAL HYPEROXIA AND OUTCOME IN SUBSETS OF CRITICAL ILLNESS: A SYSTEMATIC REVIEW, META-ANALYSIS AND META-REGRESSION OF COHORT STUDIES

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ABSTRACT

Objective

Oxygen is vital during critical illness but hyperoxia may harm patients. Our aim was to systematically evaluate the methodology and findings of cohort studies investigating the effects of hyperoxia in critically ill adults.

Data Source

A meta-analysis and meta-regression analysis of cohort studies published between 2008 and 2015 was conducted. Electronic databases of MEDLINE, EMBASE and Web of Science were systematically searched for the keywords hyperoxia and mortality or outcome.

Study Selection

Publications assessing the effect of arterial hyperoxia on outcome in critically ill adults (≥18 years) admitted to critical care units were eligible. We excluded studies in patients with chronic obstructive pulmonary disease (COPD), extracorporeal life support or hyperbaric oxygen therapy and animal studies. Due to a lack of data, no studies dedicated to patients with acute lung injury, sepsis, shock or multiple trauma could be included.

Data Extraction

Studies were included independent of admission diagnosis and definition of hyperoxia. The primary outcome measure was in-hospital mortality and results were stratified for relevant subgroups (cardiac arrest, traumatic brain injury, stroke, post cardiac surgery and any mechanical ventilation). The effects of arterial oxygenation on functional outcome, long-term mortality and discharge parameters were studied as secondary outcomes.

Data Synthesis

Twenty-four studies were included of which five studies were only for a subset of the analyses. Nineteen studies were pooled for meta-analyses and showed that arterial hyperoxia during admission increases hospital mortality: adjusted odds ratio 1.21 [95% CI 1.08–1.37] (P=0.001). Functional outcome measures were diverse and generally showed a more favorable outcome for normoxia.

Conclusions

In various subsets of critically ill patients, arterial hyperoxia was associated with poor hospital outcome. Considering the substantial heterogeneity of included studies and the lack of a clinical definition, more evidence is needed to provide optimal oxygen targets to critical care physicians.

INTRODUCTION

Oxygen supply is part of the routine treatment in critically ill patients and one of the most effective lifesaving strategies in emergency situations. During acute conditions such as cardiac arrest, myocardial ischemia, traumatic brain injury and stroke, oxygen is typically administered in a liberal manner in the pre-hospital setting. When patients survive the initial phase of such life-threatening diseases, the majority is admitted to the intensive care unit (ICU), mechanically ventilated and supported with oxygen. During ICU stay, applied fractions of oxygen (FiO_2) typically exceed accustomed concentrations of ambient air and critically ill patients often achieve supranormal arterial oxygen levels (PaO_2) in the first 24 hours of admission (1, 2). In this setting, hyperoxia may compensate and prevent tissue hypoxia by promoting oxygen delivery to the affected organs. However, arterial hyperoxia has also been shown to induce vasoconstriction and reduce cardiac output which may impair blood flow to the organs at risk (3-5). In addition, hyperoxia facilitates a complex pro-inflammatory response and has been associated with cell injury by reactive oxygen species (ROS) (6, 7). Accordingly, oxygen therapy yields a delicate balance between benefit and harm, depending on dose, duration and underlying diseases.

In critically ill patients, the harmful effects are accentuated and may eventually prevail, considering the extended duration of supplemental oxygen and the patient's susceptibility for inflammation and cardiovascular instability. In recent years, an increasing number of studies have investigated the association between arterial hyperoxia and (functional) outcome in these patients. The purpose of this review was to perform a meta-analysis and meta-regression of cohort studies comparing hyperoxia to normoxia in critically ill adults.

MATERIALS AND METHODS

This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (8). Eligibility criteria included observational cohort studies assessing the effect of arterial hyperoxia on outcome in critically ill adults (≥18 years) admitted to critical care facilities (e.g. ICU, CCU).

Data Sources and Searches

After consultation of a librarian, the electronic databases of MEDLINE (1962-2015), EMBASE (1970-2014) and Web of Science (1970-2014) were systematically searched by combining the key words and MeSH headings *hyperoxia* and *mortality* or *outcome*. Related synonyms, alternatives and plural (e.g. hyperoxaemia, arterial oxygen tension, oxygen supply, outcome, survival, fatality) were also considered. The main search was performed in July 2014 and updated in January 2015. In addition, personal records and reference lists of relevant articles were screened. The full electronic search string is shown in the supplemental data (Supplemental Digital Content 1).

Study Selection

Studies were independently screened based on title and abstract by two authors (HH, MR) and differences were resolved by consensus. We excluded studies in chronic obstructive pulmonary

disease (COPD) patients, patients on extracorporeal life support and patients undergoing surgery at the time of oxygen sampling. Data from studies with hyperbaric oxygen therapy were not considered.

We retrieved full text of potentially eligible articles. Data from full-text articles were preferred in case of duplicate reports with concurrent data in conference abstracts. Published conference abstracts were only included when requisite data for quality assessment of the database was available. No language restrictions were applied. As no formal definition for hyperoxia exists, we included studies independent of admission diagnosis and definition of arterial hyperoxia.

Data Extraction and Quality Assessment

Relevant data were extracted using a standardized data abstraction sheet. The primary outcome measure was in-hospital mortality. The effects of arterial oxygenation on functional outcomes, long-term mortality and discharge parameters were also noted as secondary outcomes. Predictive scores, including the Cerebral Performance Category (CPC), Glasgow Coma Scale (GCS) and the modified Rankin Scale (mRS), were used as a surrogate for functional outcome. Corresponding authors of included articles were contacted or data from prior analyses (9) were used in case of missing requisite data.

Quality scoring for observational studies is controversial and may lack validity and value (10). Therefore, risk of bias was estimated according to the Newcastle-Ottawa quality assessment scale (11), but no summary score for study quality was adopted. Furthermore, the studies substantially differed in methodology in terms of study population and definition of hyperoxia. Hence, results were stratified and if possible analyzed separately for subgroups, hyperoxia thresholds, selection of PaO_2 measurement and secondary outcomes.

Data Synthesis and Analysis

Effect estimates were primarily presented as adjusted odds ratios. Unadjusted odds ratios were used in absence of adjusted odds ratios, and for formal meta-analysis of the data. Odds ratios with 95% confidence intervals were pooled in a random effects model according to Mantel and Haenszel for crude effects and inverse variance for adjusted effects.

Heterogeneity was assessed, using the I^2 statistics, Chi^2 test, Tau^2 and by visualization in a funnel plot, respectively. Small study effect was visually estimated by symmetry in funnel plots. The subgroup of any mechanically ventilated patients was excluded when analyzing the crude effects in view of the heterogeneous illness severity of this population (12, 13). In case of overlapping study populations (14, 15), individuals were only counted when included in a non-overlapping time period. As a random effects model was used and in view of the model's reliability, pooled subgroup estimates were only reported in the results when five or more studies were included. In accordance, the I^2 statistics for subgroup analyses were omitted in case of few studies in order to avoid overestimation of this measure. For purposes of exploring heterogeneity, adjusted odds ratios were also graphically presented stratified by admission diagnosis, selection of PaO_2 measurement and secondary outcomes. The effects of hyperoxia by threshold were, independent of admission diagnosis, analyzed using a meta-regression framework (16). Mixed effects models were performed

with subgroup, threshold, and timing and selection of the PaO_2 measurement as predictors for outcome. In these moderator analyses, threshold was categorized according to the primary PaO_2 cut-off used for defining hyperoxia. Subgroups were categorized as the subsets of critically ill patients. The selection of the PaO_2 measurement was categorized as first, worst, highest or mean and the timing was defined as measurement within or beyond 24 hours of admission.

Analyses were conducted with RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio version 0.98.1028 (RStudio Inc, Boston, MA).

RESULTS

Search Results and Study Characteristics

Our search strategy resulted in 1609 studies considered for inclusion. After screening of titles and abstracts 32 full-text articles were assessed for eligibility (Fig. 1).

In total, 24 cohort studies were included, of which five studies were included only for specific subset analyses or for secondary outcomes (Table 1). The included articles were published between 2008 and 2015 and data collection was conducted between 1987 and 2012. In total, twelve articles included cardiac arrest patients, five included patients with traumatic brain injury (TBI), three included stroke patients, one included post cardiac surgery patients, and the remaining two studies included mechanically ventilated ICU patients, independent of admission diagnosis. The estimated risk of bias of included studies was moderately low. Most studies used large and high quality national databases and adjusted the data for severity of illness. Two studies did not adjust the data for potential confounders (17, 18) and two studies included cardiac arrest patients only when treated with therapeutic hypothermia (19, 20).

Qualitative Data Synthesis

Adjusted odds ratios for the primary outcome ranged from 0.11 to 2.00 (Supplemental Table 1, Supplemental Digital Content 2).

Frequent confounders included in multivariate analysis were age, sex, illness severity, and subgroup specific confounders such as neurological or cardiac parameters. The most commonly used threshold to define hyperoxia was 300 mmHg (range 85–487 mmHg), although cohort specific thresholds based on data distribution across percentiles were also frequently chosen. The selected PaO_2 used for classification of patients were mainly based on measurements in the first 24 hours of admission in the hospital or ICU. Some studies used longer time frames (20, 29, 34) and/or estimated hyperoxia exposure from more than one blood gas sample (20, 21, 27, 30, 34). In most studies, the reference range for calculating odds ratios was chosen as self-defined normoxia range. In a few studies hyperoxia was compared to non-hyperoxia (17, 26).

Some studies were not pooled in the meta-analyzed models, due to missing requisite crude (12, 13, 18, 21, 25-27) and/or adjusted data (17, 34) for the primary outcome. One study (24) was excluded for meta-analysis in order to prevent duplicate data synthesis as this study used a secondary analysis of another included cohort (23).

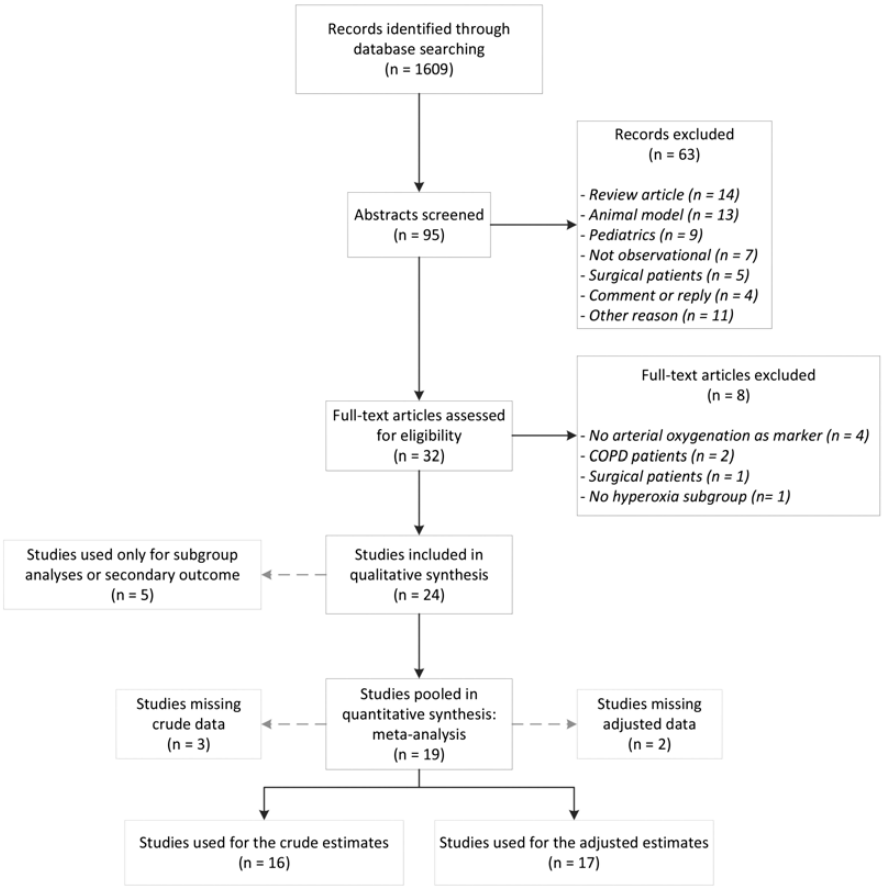

Figure 1. Flow diagram of study selection for the systematic review.
COPD, chronic obstructive pulmonary disease.

Quantitative Data Synthesis

Meta-analysis of sixteen studies covering 49,389 patients showed a crude odds ratio of 1.38 [95% CI 1.18–1.63] (P<0.0001) for in-hospital mortality, independent of admission diagnosis (Fig. 2). This corresponds with a risk ratio of 1.18 [95% CI 1.08–1.30] and a risk difference of 0.06 [95% CI -0.02–0.13]. The overall effects were statistically significant in subgroups of cardiac arrest (P=0.001) and ischemic stroke (P=0.03), but not for TBI (P=0.32), subarachnoid (P=0.47), intracerebral hemorrhage (P=0.09) and post cardiac surgery (P=0.19). Heterogeneity among all studies was substantial (I^2 76%), but unimportant among subgroups (I^2 0%).

Meta-analysis of adjusted estimates derived from seventeen studies showed an odds ratio of 1.21 [95% CI 1.08–1.37] (P=0.001) (Fig. 3). The tests for overall effect was only statistically significant for cardiac arrest patients (P=0.005). Again, heterogeneity among all studies was considerable (I^2 80%), and moderate among subgroups (I^2 41%).

Table 1. Characteristics of included studies sorted by subgroup

Author	Year	Country	Data collection	Subgroup	Setting	Inclusion period	Cohort size	Oxygen Supply	Remarks
de Jonge (12)	2008	The Netherlands	Retrospective	Any mechanical ventilation Subsample	ICU	1999-2006	36307	MV	High quality database
Eastwood (13)	2012	Australia/New Zealand	Retrospective	Any mechanical ventilation	ICU	2000-2009	152680	MV	High quality database
Bellomo (14)	2011	Australia/New Zealand	Retrospective	Cardiac arrest (non-traumatic)	ICU	2000-2009	12108	MV / SB	High quality database
Elmer (21)	2015	USA	Prospective	Cardiac arrest (all with ROSC)	-	2008-2010	184	MV	High quality database
Helmerhorst (22)	2014	The Netherlands	Retrospective	Cardiac arrest (non-traumatic)	ICU	2007-2012	5258	MV	High quality database Conference abstract
Ihle (15)	2013	Australia	Retrospective	Cardiac arrest (ventricular fibrillation)	ICU	2010-2011 2007-2011	207 584[a]	MV / SB	High quality database
Janz (19)	2012	United States	Prospective	Cardiac arrest (mild therapeutic hypothermia)	CCU	2007-2012	170	MV	Specific subgroup
Kilgannon (23)	2010	United States	Retrospective	Cardiac arrest (non-traumatic)	ICU	2001-2005	6326	MV / SB	High quality database
Kilgannon (24)[a]	2011	Unites States	Retrospective	Cardiac arrest (non-traumatic)	ICU	2001-2005	4459	MV / SB	High quality database
Lee (20)	2014	Republic of Korea	Retrospective	Cardiac arrest (therapeutic hypothermia)	-	2008-2012	213	-	Specific subgroup
Nelskyla (17)	2013	Australia	Prospective	Cardiac arrest (all with ROSC)	ICU	2008-2010	122	MV / SB	No adjustment for confounders
Roberts (25)[a]	2013	United States	Prospective	Cardiac arrest (non-traumatic)	-	2009-2011	193	MV	High quality database

Table 1. (continued)

Author	Year	Country	Data collection	Subgroup	Setting	Inclusion period	Cohort size	Oxygen Supply	Remarks
Schneider (26)[a]	2013	Australia/New Zealand	Retrospective	Cardiac arrest (non-traumatic)	ICU	2000-2011	16542	MV	High quality database
Spindelboeck (18)[a]	2013	Austria	Retrospective	Cardiac arrest (non-traumatic)	CPR	2003-2010	145	MV	No adjustment for confounders
Vaahersalo (27)[a]	2014	Finland	Prospective	Cardiac arrest (out-of-hospital)	ICU	2010-2011	409	MV	High quality database
Sutton (28)	2014	Australia/New Zealand	Retrospective	Post cardiac surgery	ICU	2003-2012	83060	MV / SB	High quality database
Asher (29)	2013	United States	Retrospective	Traumatic brain injury	-	-	193	-	-
Brenner (30)	2012	United States	Retrospective	Traumatic brain injury	-	2002-2007	1547	-	-
Davis (31)	2009	United States	Retrospective	Traumatic brain injury	-	1987-2003	3420	-	-
Raj (32)	2013	Finland	Retrospective	Traumatic brain injury	ICU	2003-2012	1116	MV	High quality database
Rincon (33)	2013	United States	Retrospective	Traumatic brain injury	ICU	2003-2008	1212	MV	High quality database
Jeon (34)	2014	United States	Retrospective	Subarachnoid hemorrhage	-	1996-2011	252	MV	-
Rincon (35)	2014	United States	Retrospective	Stroke Ischemic stroke Subarachnoid hemorrhage Intracerebral hemorrhage	ICU	2003-2008	2894 554[a] 936[a] 1404[a]	MV	High quality database
Young (36)	2012	Australia/New Zealand	Retrospective	Ischemic stroke	ICU	2000-2009	2643	MV	High quality database

MV, mechanical ventilation, SB, spontaneously breathing, ROSC, return of spontaneous circulation.
[a] Records are included for specific subgroup analyses or for secondary outcomes.
Dashes indicate not specifically stated.

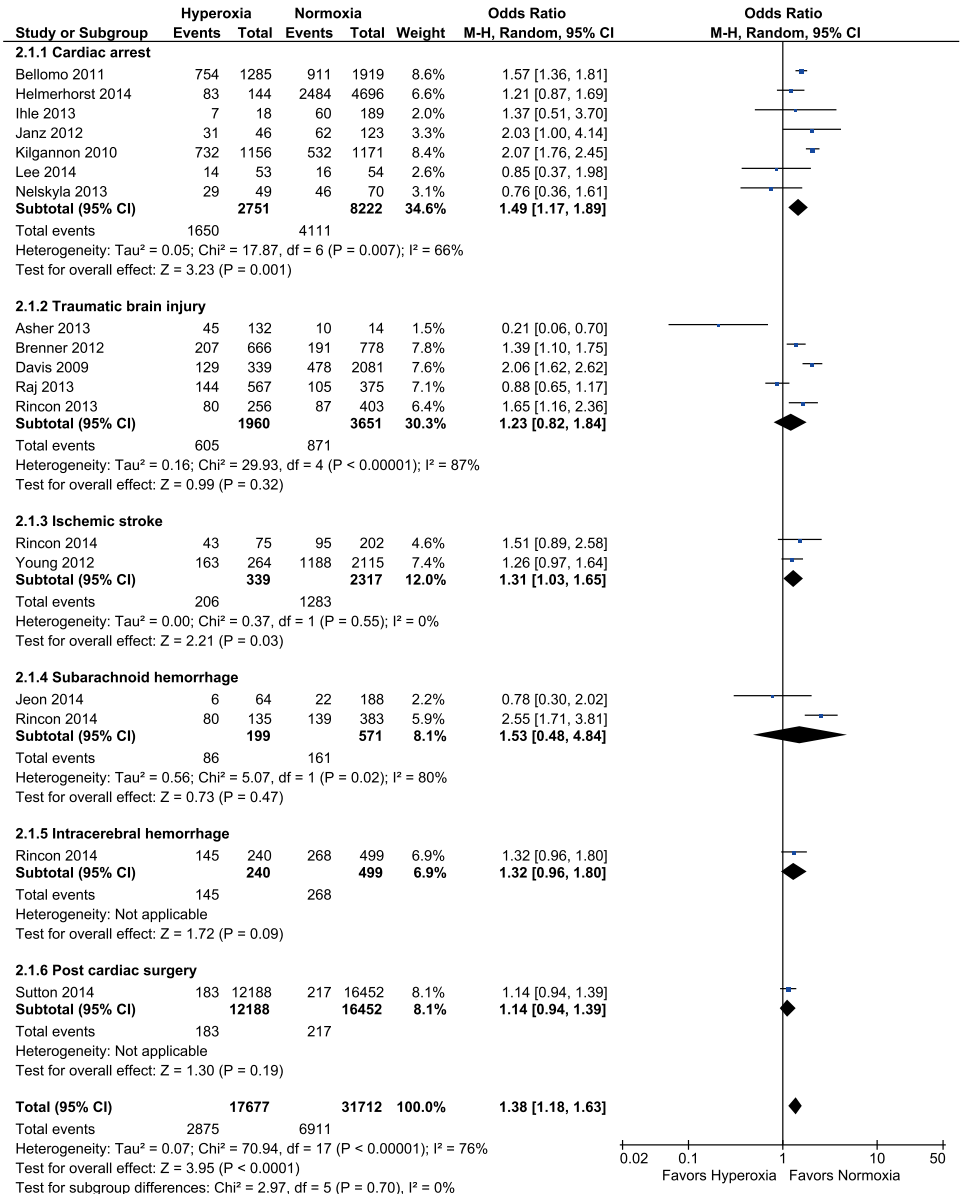

Figure 2. Forest plot for the crude associations between arterial hyperoxia and hospital mortality by subsets of critical illness.

The pooled odds ratios were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimates. CI, confidence interval, M-H, Mantel-Haenszel.

Adjusted odds ratios for mechanically ventilated patients (n=2 studies) were 1.00 [95% CI 0.94–1.07] and 1.23 [95% CI 1.13–1.34]. In cardiac arrest patients, the adjusted odds ratios (n=6 studies) ranged from 0.60 to 1.80, with a pooled estimate of 1.31 [95% CI 1.09–1.57] (I^2 63%). In patients with

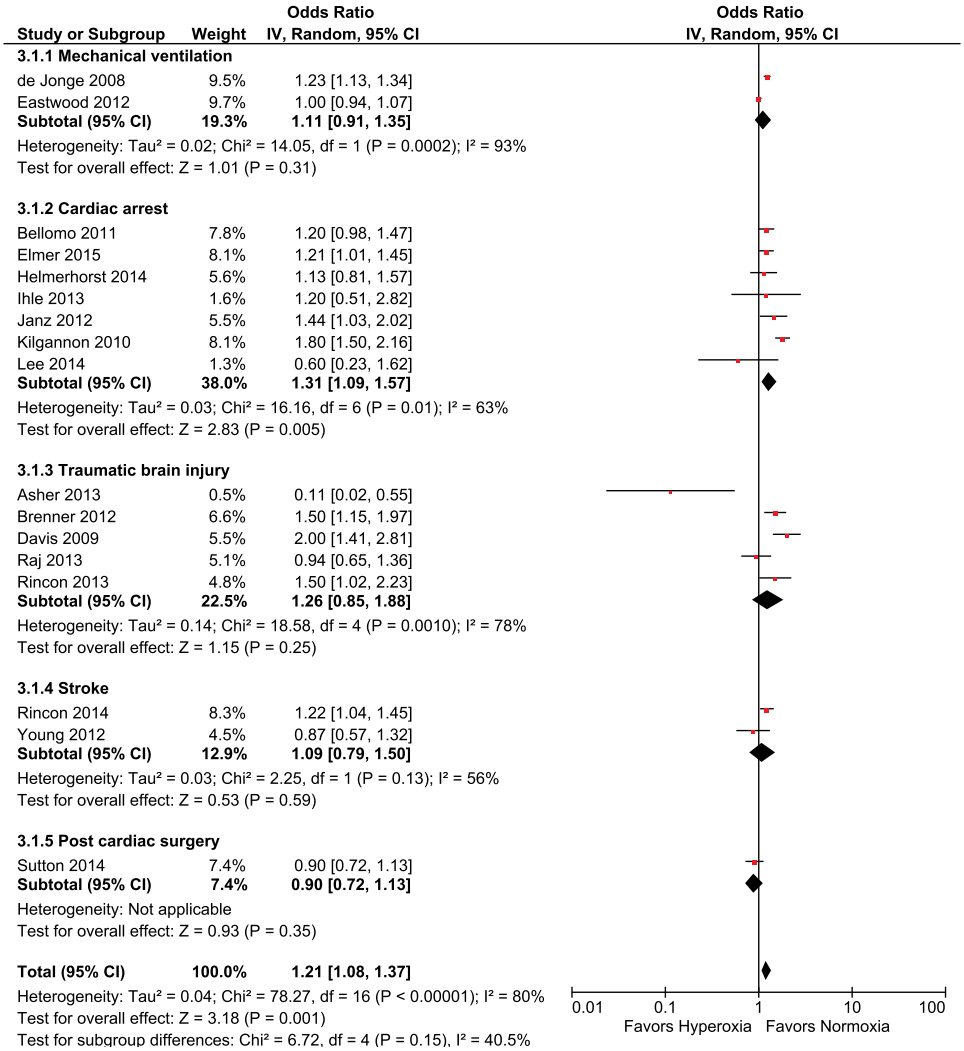

Figure 3. Forest plot for the adjusted associations between arterial hyperoxia and hospital mortality by subsets of critical illness.

The pooled odds ratios were calculated using a random-effects model. Weight refers to the contribution of each study to the pooled estimates. CI, confidence interval, IV, inverse variance.

TBI, adjusted odds ratios (n=5 studies) ranged from 0.11 to 2.00, with a pooled estimate of 1.26 [95% CI 0.85–1.88] (I^2 78%). Stroke patients were combined and adjusted odds ratios (n=2 studies) were 0.87 [95% CI 0.57–1.32] and 1.22 [95% CI 1.04–1.45]. In post cardiac surgery patients, the odds ratio (n=1) was 0.9 [95% CI 0.7–1.1].

The crude (Figure 4a) and adjusted (Figure 4b) effect estimates increased with increasing thresholds used for defining arterial hyperoxia (P=0.007 and P=0.22, respectively) and showed a significant difference between threshold categories (P<0.00001).

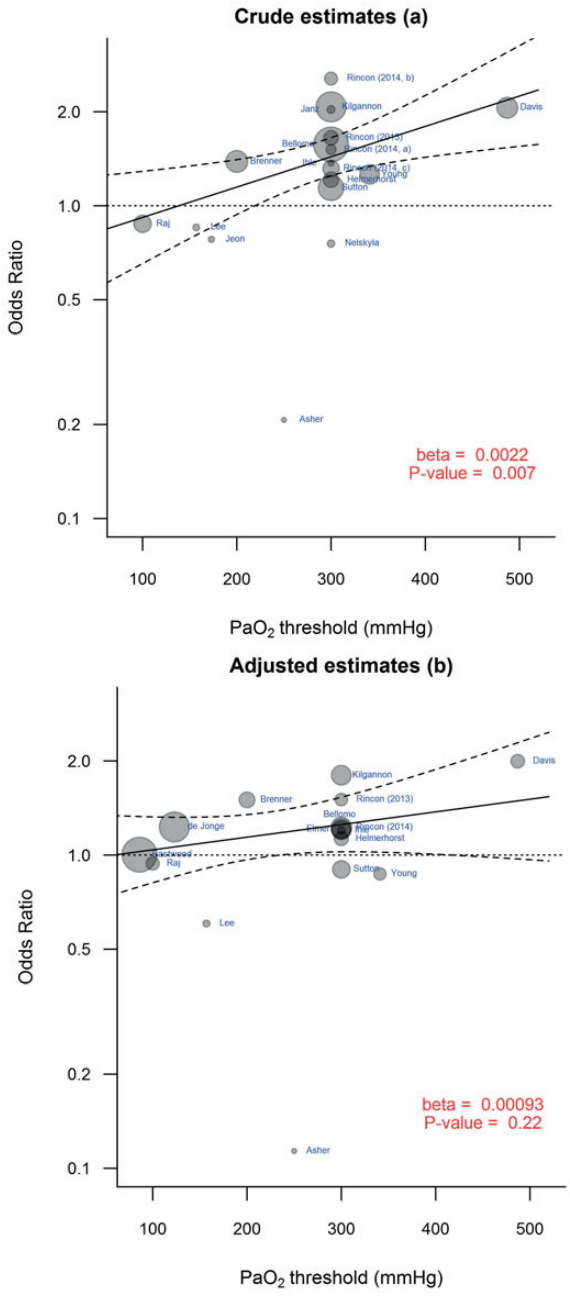

Figure 4. Meta-regression analysis for the crude (**a**) and adjusted (**b**) effects on hospital mortality by PaO_2 threshold.

Scatters indicate odds ratios for in-hospital mortality on a logarithmic scale, according to the hyperoxia threshold that was used as primary cutoff in the indicated studies. The point sizes are inversely proportional to the SEs of the individual studies (i.e., larger/more precise studies are shown as larger *circles*). The predicted effect sizes are modeled in a linear mixed-effects model with corresponding 95% CI boundaries and a β-coefficient with *p* value for the meta-regression line.

Figure 5 displays the effects stratified for selection of the PaO_2 measurement and also showed significant subgroup differences (P<0.001). When modeling the crude effects, subgroup (P=0.001), threshold (P=0.01) and timing and selection of the PaO_2 measurement (P=0.01 and P=0.003, respectively) were independent moderators of the outcome. The individual tests of moderators were not significant when modeling the adjusted estimates.

The symmetrical appearance of the funnel plots (Supplemental Fig. 1, Supplemental Digital Content 3 and Supplemental Fig. 2, Supplemental Digital Content 4) indicates that substantial publication bias is unlikely. Also, studies finding either statistically significant or non-significant

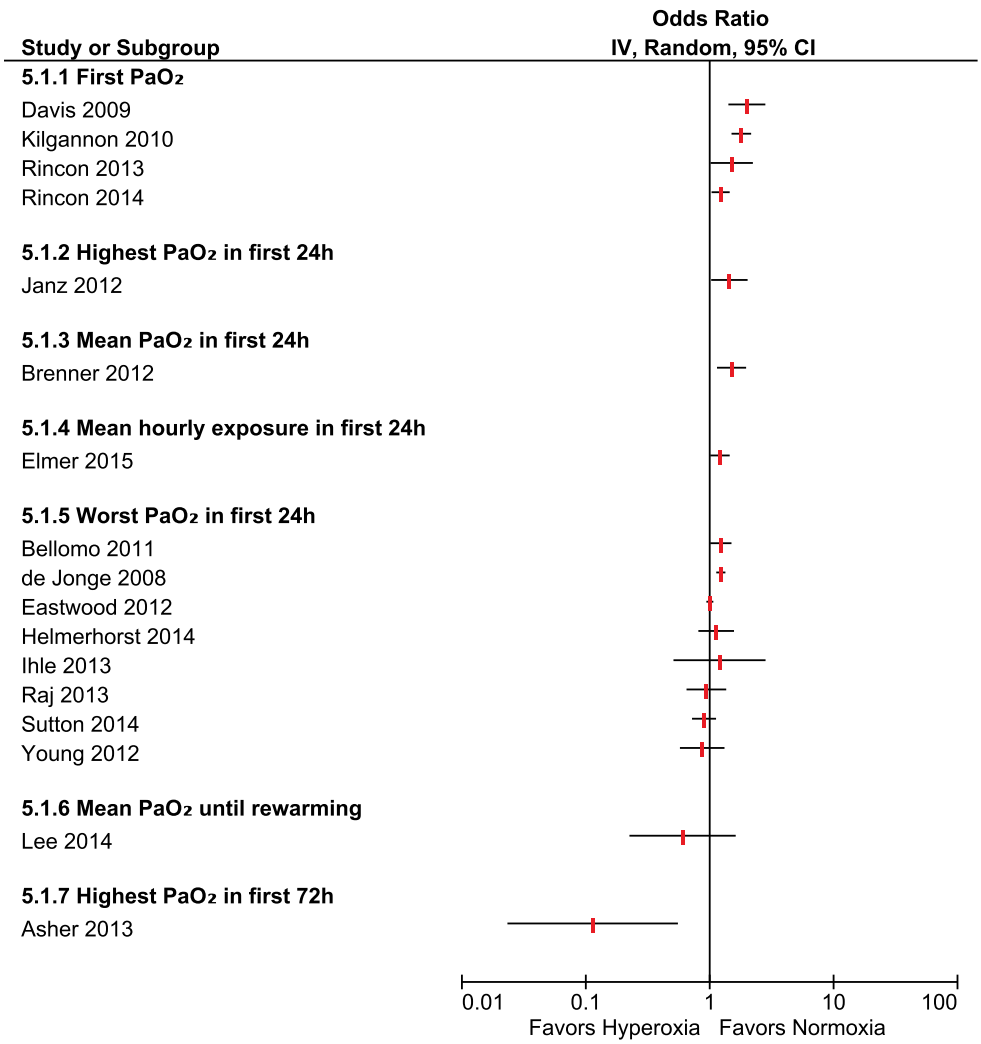

Figure 5. Forest plot for the adjusted effects of arterial hyperoxia by selection of PaO_2 measurements. Subgroups sorted in ascending order by timing and selection of PaO_2 measurements. Studies sorted alphabetically by name of first author.

effects were almost equally published and had a similar mean publication delay (129 vs. 121 days, respectively, P=0.68) (supplemental data, Supplemental Digital Content 1).

Secondary outcomes were diverse and results are listed in the Supplemental Table 2 (Supplemental Digital Content 5). Significant associations of adjusted analyses were found for CPC≥3 (cardiac arrest), GCS 3-8 (TBI), mRS 4-8 and delayed cerebral ischemia (stroke) (Fig. 6). Arterial hyperoxia was associated with hospital stay shorter than 7 days in TBI patients, although this association did not reach statistical significance for ICU stay in the same cohort (30), nor in

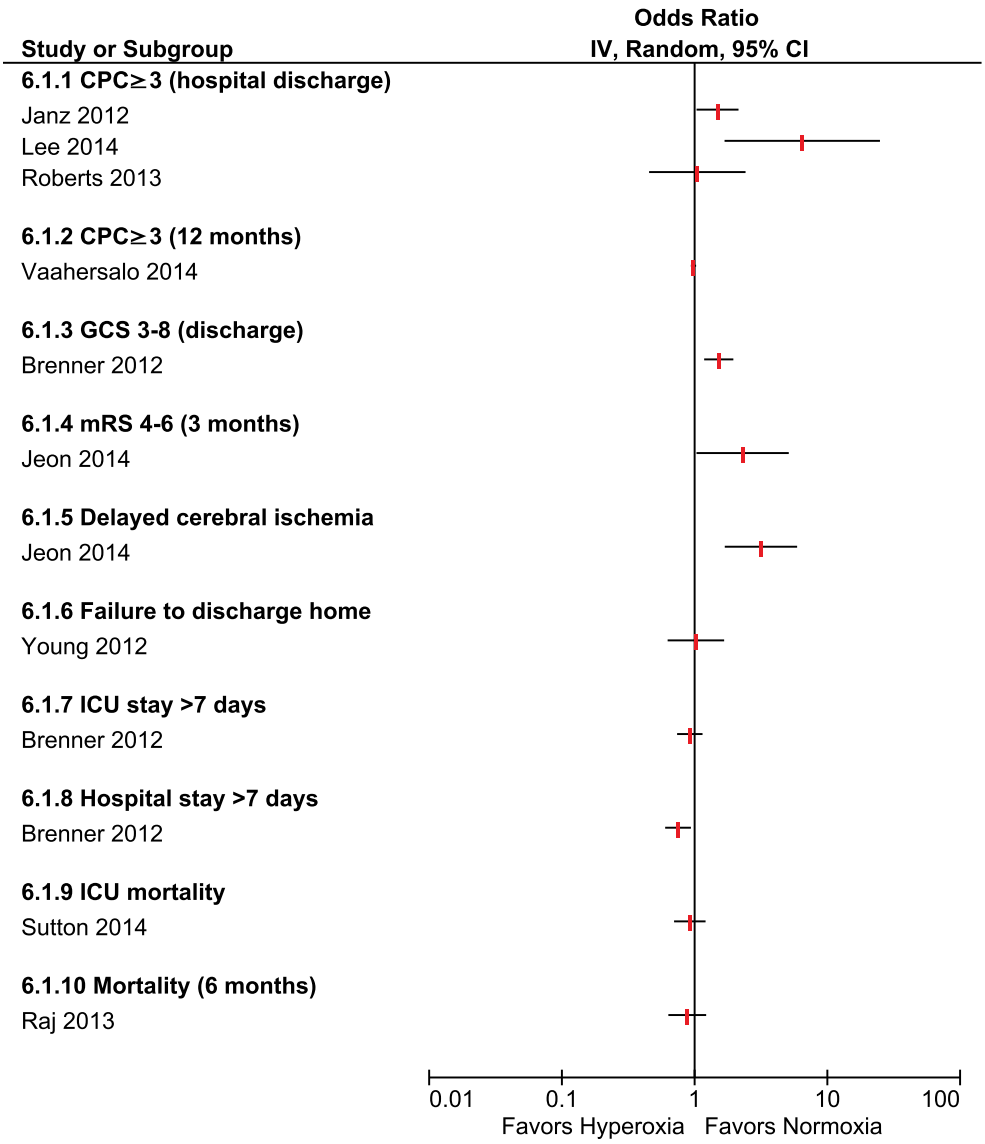

Figure 6. Forest plot for the adjusted effects of arterial hyperoxia by secondary outcomes.
CPC, Cerebral Performance Category, GCS, Glasgow Coma Scale, mRS, modified Rankin Scale.

a prospective cohort of cardiac arrest patients (17). ICU mortality, 6 month-mortality and failure to discharge home were not significantly associated with arterial hyperoxia (17, 26, 28, 32, 36).

DISCUSSION

This systematic review identified nineteen observational cohort studies investigating the crude and/or adjusted effects of arterial hyperoxia on hospital mortality in major subgroups of critically ill patients. Meta-analysis of pooled data from all patients highlighted that arterial hyperoxia was associated with hospital mortality. After adjustment for confounders, this association was also established in patients admitted to critical care units following cardiac arrest, but this effect was not found in other subgroups. Functional outcome measures were diverse and showed a signal generally favoring normoxia. Other secondary outcomes were not associated with arterial hyperoxia. However, considerable heterogeneity and the observational character of included studies hamper profound conclusions and causal inferences.

The observed heterogeneity warrants cautious interpretation of pooled results. Our findings may be substantially influenced by the used methodology of the included studies and stress the importance of the used threshold, reference range, confounders, summary statistic, subgroup and outcome measure. The definition of hyperoxia and its reference range may be the most important factors determining the effect size. Indeed, increasing PaO_2 levels were more strongly associated with poor outcome, but this observation may have been attenuated by detrimental effects of hypoxia, in cases where this subgroup was not excluded from the reference group. Moreover, the prevalence of hyperoxia was highly dependent on the used threshold and also addresses the relevance of the risks of severe hyperoxia in different cohorts. The timing and selection of the PaO_2 measurement chosen to reflect arterial oxygenation emerged as another key determinant of the magnitude of the association. The choice of this summary statistic for defining hyperoxia can be essential in determining the relation between oxygenation and the outcome as oxygen toxicity may manifest during prolonged exposure, while direct effects may also be crucial in the acute and pre-hospital setting. Indeed, hyperoxia in the first arterial blood gas was more consistently associated with poor outcome than averaged oxygen levels, which may in fact not be a reliable marker of the total hyperoxic exposure during ICU stay. These findings suggest that oxygen may have both a time and dose dependent effect in which early (first samples) and severe hyperoxia are specifically hazardous. However, we cannot rule out that hyperoxia can also be harmful during prolonged exposure and when PaO_2 values are moderately higher than normal.

The study by Asher et al. (29) contradicts most other findings and is likely to be an outlier as a result of its small sample size which is also reflected in the funnel plots and by its weight in meta-analyses. Further, it is the only study to use the highest PaO_2 in the first 72 hours of admission, which may represent other oxygenation and ventilation strategies during this phase of admission than other summary statistics. Despite the addressed differences between all included studies, the direction of the pooled effects pertains, while the magnitude and significance level of individual results may be partially explained by methodological issues.

The following study strengths and limitations should be considered. First, well established confounders for outcome after ICU stay (e.g. illness severity scores), cardiac arrest (e.g. initial

rhythm), TBI and stroke (e.g. Glasgow Coma Scale, Injury Severity Score), were assessed in some but not all included studies and may substantially determine the effect size. Moreover, authors should judiciously consider to recalculate illness severity scores when included as a confounder in multivariate analyses. These scores may contain the same PaO_2 derived from the first 24 hours of admission as the PaO_2 that is used for defining hyperoxia as outcome predictor. A recalculated score, omitting or standardizing oxygen components, may therefore avoid overadjustment in such analyses. In line, FiO_2 levels are closely related to PaO_2 levels, included in illness severity scores and may accordingly inflict multicollinearity.

Unmeasured bias may impose a further limitation inherent to analyses in observational studies. From the funnel plots, we cannot fully rule out that our findings are impacted by publication bias. On the other hand, the statistical significance level of the results did not appear to have an effect on publication delay and we also included data from a conference abstract study where database quality was previously assessed (37). Partially overlapping populations (14, 15, 26) (23, 24) in databases from included studies was accounted for by including only the main study in meta-analysis and by presenting the data as a subsample, where appropriate.

Experimental data from animal models have recently been summarized and showed an association between 100% oxygen therapy and worse neurological outcome following cardiac arrest (38). In accordance, aggregated data from observational studies focusing on cardiac arrest patients found a correlation between hyperoxia and hospital mortality (9). A recent meta-analysis found insufficient evidence regarding the safety of arterial hyperoxia, as the results may be impacted by methodological limitations (39). The current analyses extend these observations by including and aggregating all subgroups including post-operative cases, various secondary outcomes, novel data from recent cohort studies and by further exploring the impact of the definition of hyperoxia. Still, our findings may not depict a universal effect for all ICU patients and cannot be directly extrapolated to other subgroups.

Current guidelines aim at PaO_2 levels around 55 to 80 mmHg, but this target range was based on expert-consensus more than on evidence from clinical studies (40, 41). Conflicting findings from previous studies further impede the constitution of compelling clinical recommendations. Consequently, attitudes regarding the management of oxygen administration vary considerably and clinicians often consider hyperoxia acceptable as long as the FiO_2 is relatively low (1, 42). This may also be triggered by the double-edged nature of oxygen, which similarly urges strict prevention of hypoxia and its inherent hazards (12, 13). Furthermore, carbon dioxide may importantly mediate the effects of oxygen, although direct effects are assumed to be small (43). Hyperoxia may alternatively be a non-causal marker of disease severity as clinicians may intuitively treat the most severely ill patients with higher FiO_2 or PEEP levels in attempts to compensate for tissue hypoxia. Although this is less likely as the association between hyperoxia and mortality has also been shown to persist after adjustment for severity scores and FiO_2, future prospective intervention trials are needed to definitively study the effects of hyperoxia on outcome.

CONCLUSIONS

This systematic review has shown that, despite methodological limitations, arterial hyperoxia is associated with poor hospital outcome in various subsets of critically ill patients. The harmful effects depend on hyperoxic degree and may be more pertinent to certain subgroups at specific moments of admission. Taken together, the effect estimates favoring normoxia were quite consistent throughout our analyses, but were not universal for all subsets and secondary outcomes. In the absence of studies specifically addressing the effects in other important critical care subgroups, including acute lung injury, sepsis, shock and multiple trauma, the vast majority of the population in the current analysis consisted of patients with mechanical ventilation, cardiac arrest, traumatic brain injury and stroke. Furthermore, the impact of pursuing normoxia on the incidence of hypoxic episodes is unknown and the long-term effects of conservative oxygen therapy are still to be assessed in large cohorts. Given the lack of robust guidelines, more evidence is needed to provide tailored oxygen targets for critically ill patients.

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6a

TO THE EDITOR: ASSOCIATION BETWEEN HYPEROXIA AND MORTALITY AFTER CARDIAC ARREST

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We read the article by Helmerhorst et al. (1) with interest. Hyperoxia has been studied in emergency situations, such as cardiac arrest (CA), myocardial ischemia, traumatic brain injury, and stroke. The potential harm of hyperoxia due to the oxygen free radical formation has been discussed in several studies. Because of the diversity of diseases and the different definitions of hyperoxia, these conclusions remain contradictory.

In this review, seven studies about CA have been pooled to investigate the association between hyperoxia and mortality. Because of the diversity of methodology, definitions of hyperoxia, reference range, and other confounders, the heterogeneity was significant (I^2 = 66%), which warrants cautious interpretation of the pooled results.

In a sensitivity analysis of this pooled outcome, we found that when the study by Bellomo et al. (2) was excluded, the conclusion became insignificant (odds ratio, 1.38; 95% CI, 0.95–2.01; I^2 = 70%) (**Fig. 1**).

This may be explained that Bellomo et al. (2) chose the lowest PaO_2 level or the PaO_2 associated with the arterial blood gas with the highest alveolar-arterial gradient, which may lead to the underestimation of the proportion of hyperoxia. According to the conclusion of Kilgannon et al. (3), there was a dose-dependent association between mortality and PaO_2 range, with a 24% increase in mortality risk for every 100 mmHg increase in PaO_2, which means that in the study by Bellomo et al. (2), the mortality associated with hyperoxia may be overestimated.

Besides, in the study by Kilgannon et al. (4) based on IMPACT database, a large critical-care database of ICU at 120 U.S. hospitals initially developed by the Society of Critical Care Medicine, the first blood gas measurement in the ICU was used and found that hyperoxia (PaO_2 of at least 300 mmHg) was associated with increased mortality. This excluded the temporal effect of hyperoxia, which has been debated whether the use of blood gas value at a single time point was appropriate.

In this sensitivity analysis, when the study by Kilgannon et al. (4) was excluded, the heterogeneity became insignificant, with I^2 decreasing from 66% to 33%, which raised the question: Is it appropriate to include this study in this analysis? In the reanalysis of IMPACT database by Kilgannon et al. (3), they defined the exposure by the highest partial pressure of arterial oxygen over the first 24 hours

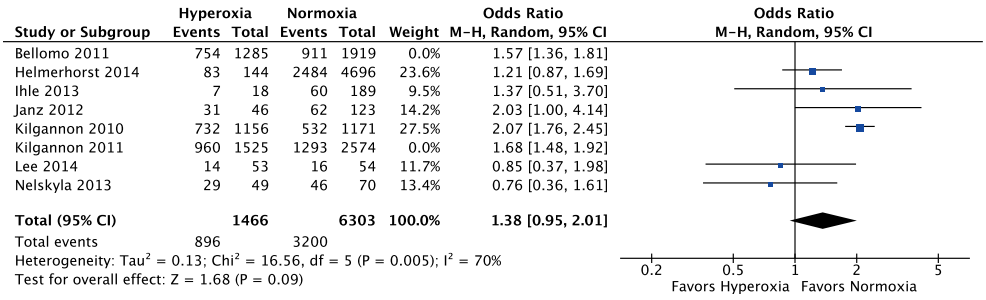

Figure 1. Sensitivity analysis of association between hyperoxia and mortality (Bellomo et al (2) was excluded). M-H, Mantel-Haenszel.

in the ICU, with the same inclusion and exclusion criteria of Kilgannon et al. (4). Because of different data acquisition time, the number of patients was slightly different. We extracted the mortality from Figure 1 in this article, with definition of hyperoxia as PaO_2 of at least 300 mmHg, and reanalyzed in Review Manager 5.1.6. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). The heterogeneity become insignificant (I^2 = 37%) (**Fig. 2**), and the sensitive analysis was stable.

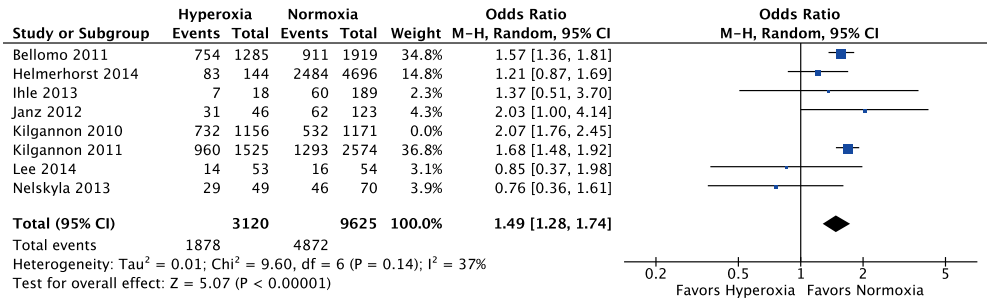

Figure 2. Reanalysis of association between hyperoxia and mortality (Kilgannon et al (4) was replaced by Kilgannon et al (3)). M-H, Mantel-Haenszel.

Based on current studies, hyperoxia was associated with increased mortality in CA patients; because of the diversity definition of hyperoxia in these studies, the pooled results should be interpreted with caution.

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6b

THE AUTHORS REPLY

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We thank Shen and Zhang (1) for their interest and thoughtful analyses regarding our work. Their sensitivity analyses provide valuable insights in the relationship between arterial hyperoxia and hospital mortality after cardiac arrest and further emphasize the importance of the used definition for arterial hyperoxia. As discussed in our study (2), we strongly agree that the pooled results must be interpreted with caution in view of the observed heterogeneity.

The selection of a single PaO_2 yields considerable limitations and the time point at which the arterial blood gas was analysed may further lead to misinterpretation of the actual exposure to hyperoxia during ICU admission. Indeed, we showed that both timing and selection were independent moderators of the outcome when modeling the crude effects (2). Sensitivity analyses are useful alternatives to examine the impact of individual study results and methodology. The abstraction of arterial hyperoxia that was used in the studies by Bellomo et al. (3) and Kilgannon et al. (4) may indeed not be the most representative method, but the rationale for an eventual exclusion of these studies in analyses should also be carefully considered.

First, similar methods using the first, lowest or worst PaO_2 during admission were also frequently used in other cohorts and have not previously been shown to be inferior. Second, after exclusion of the study by Bellomo et al. (3), the recalculated pooled effect estimate reflects statistical insignificance by the strict use of statistical thresholds, but the absolute difference between the original estimate and the estimate in sensitivity analyses was actually marginal (odds ratio difference, 0.11) and showed a slight shift in magnitude yet not in direction. The shift in effect size should rather be interpreted as a loss of statistical power considering the size of the excluded cohort. This is also supported by the adjusted analyses, which may be used to overcome several other study limitations. When the study by Bellomo et al. (3) was excluded in sensitivity analyses using adjusted effect estimates, the pooled effects remained virtually unchanged (adjusted odds ratio, 1.32; 95% CI, 1.05–1.66 vs adjusted odds ratio, 1.31; 95% CI, 1.09–1.57). It can be debated whether this study essentially overestimated the mortality. The authors have comprehensively stratified the risks by deciles of PaO_2, whereas we selected only the reported risk estimate according to the primarily used threshold of hyperoxia (i.e., 300 mmHg). Their results have previously been compared with the Kilgannon studies, and other methodological differences may explain heterogeneity (5). It is yet interesting to note that the replacement of the original Kilgannon study data (4) by their secondary analysis reduces the heterogeneity, which may be attributed to the use of the highest PaO_2 in concordance with the study by Janz et al. (6). Nonetheless, the recalculated pooled effect estimates did not materially differ, which may in fact not be overly surprising because the data were generated from a subsample of the same cohort.

Finally, the temporal effect of hyperoxia has not been adequately accounted for in most studies and is typically only estimated within the first 24 hours of admission. The exact impact over the total ICU admission remains unknown although we have initiated comprehensive analyses comparing different strategies for defining hyperoxia. Preliminary results of such analyses in a Dutch multicenter cohort of ICU patients suggest that all strategies differ substantially, and results should therefore always be viewed in light of the used definition for arterial hyperoxia.

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7

METRICS OF ARTERIAL HYPEROXIA AND ASSOCIATED OUTCOMES IN CRITICAL CARE

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ABSTRACT

Objective

Emerging evidence has shown the potential risks of arterial hyperoxia, but the lack of a clinical definition and methodological limitations hamper the interpretation and clinical relevance of previous studies. Our purpose was to evaluate previously used and newly constructed metrics of arterial hyperoxia and systematically assess their association with clinical outcomes in different subgroups in the intensive care unit (ICU).

Design

Observational cohort study

Setting

Three large tertiary care ICUs in the Netherlands

Patients

A total of 14,441 eligible ICU patients

Interventions

None

Measurements and Main Results

In total, 295,079 arterial blood gas (ABG) analyses, including the partial pressure of arterial oxygen (PaO_2), between July 2011 and July 2014 were extracted from the patient data management system database. Data from all admissions with more than one PaO_2 measurement were supplemented with anonymous demographic and admission and discharge data from the Dutch National Intensive Care Evaluation registry. Mild hyperoxia was defined as PaO_2 between 120 and 200 mmHg; severe hyperoxia as PaO_2 >200 mmHg. Characteristics of existing and newly constructed metrics for arterial hyperoxia were examined and the associations with hospital mortality (primary outcome), ICU mortality and ventilator-free days and alive at day 28 (VFDs) were retrospectively analyzed using regression models in different subgroups of patients.

Severe hyperoxia was associated with higher mortality rates and fewer VFDs in comparison to both mild hyperoxia and normoxia for all metrics except for the worst PaO_2. Adjusted effect estimates for conditional mortality were larger for severe hyperoxia than for mild hyperoxia. This association was found both within and beyond the first 24 hours of admission and was consistent for large subgroups. The largest point estimates were found for the exposure identified by the average PaO_2, closely followed by the median PaO_2 and these estimates differed substantially between subsets. Time spent in hyperoxia showed a linear and positive relationship with hospital mortality.

Conclusions

Our results suggest that we should limit the PaO_2 levels of critically ill patients within a safe range, as we do with other physiological variables. Analytical metrics of arterial hyperoxia should be judiciously considered when interpreting and comparing study results and future studies are needed to validate our findings in a randomized fashion design.

INTRODUCTION

Oxygen therapy and arterial oxygenation play a vital role in the clinical course of patients in the intensive care unit (ICU). The effects of hypoxia are well established and are actively prevented in order to maintain physiological stability. In contrast, hyperoxia is frequently encountered in the ICU but generally accepted (1-3). In recent years, emerging evidence has shown the potential risks of arterial hyperoxia (4, 5), but observational studies failed to indisputably demonstrate its impact on clinical outcomes of critically ill patients (6-9). Most studies focus on hospital mortality of mechanically ventilated patients, but the lack of a clinical definition of hyperoxia and methodological limitations hamper the interpretation and clinical relevance of these studies (10). Importantly, it is unknown whether the partial pressure of arterial oxygen (PaO_2) from a single arterial blood gas (ABG) measurement in the first 24 hours of admission reliably estimates the actual exposure to hyperoxia and associated risks during the ICU stay. Also, we do not know whether high arterial peak-levels of oxygen or prolonged exposure to high PaO_2 are associated with adverse outcomes. Knowledge on oxygenation metrics and related summary statistics is important when interpreting studies on the effects of hyperoxia and for setting up future research. Oxygenation based metrics may be based on a certain time period (e.g. first 24 hours after ICU admission or complete ICU period) and on a single measurement, central tendency or cumulative exposure.

The aim of this study was to 1) comprehensively assess the metric-related association of arterial oxygenation with clinical outcomes in different subsets of critically ill patients and 2) systematically evaluate the influence of choosing a certain metric on the composition of subgroups of patients with arterial hyperoxia and mortality in those subgroups.

MATERIALS AND METHODS

Data collection

Data were collected between July 2011 and July 2014. Data collection procedures have been described in detail previously, and reviewed and approved by the Medical Ethical Committee of the Leiden University Medical Center (2, 11). In brief, arterial blood gas (ABG) analyses and concurrent ventilator settings were extracted from the patient data management system (PDMS) database (MetaVision, iMDsoft, Leiden, The Netherlands) of closed format, mixed medical and surgical, tertiary care ICUs of three participating hospitals in the Netherlands. Data were supplemented with anonymous demographic data, admission and discharge data, and variables to quantify severity of illness from the Dutch National Intensive Care Evaluation (NICE) registry, a high quality database, which has been described previously (12). According to the Dutch Medical Research Involving Human Subjects Act, there was no need for informed patient consent, as only registries without patient identifying information were used. Admissions were only eligible for inclusion when requisite data from more than one ABG measurement was available. Patients on extracorporeal membrane oxygenation were excluded from the study. Conservative oxygenation was promoted during the study in all three units, but actual strategies were left to the discretion of the attending physicians and nurses.

Hyperoxia metrics

We calculated several previously used and newly constructed metrics for arterial hyperoxia. Existing metrics were derived from a systematic literature review and included the first, highest, worst, and average PaO_2, typically assessed over the first 24 hours of admission (9). These metrics were compared to new metrics within specific time frames, namely the median, area under the curve and time spent in arterial hyperoxia.

As no formal definition for arterial hyperoxia exists, we stratified the analyses using previously used thresholds, while considering the incidence in the present cohort. Mild hyperoxia was defined as PaO_2 120 – 200 mmHg (13) and severe hyperoxia as PaO_2 > 200 mmHg (14).

Metrics of single sampling

The first PaO_2 (FIR) was the PaO_2 value that was measured in the first ABG registered in the PDMS after the patient was admitted to the ICU.

Highest PaO_2 (MAX) was the maximum value that was registered during the first 24 hours ($MAX_{0\text{-}24}$) or during the total ICU LOS ($MAX_{ICU\ LOS}$). Worst PaO_2 (WOR) was defined as the PaO_2 derived from the ABG associated with the lowest concurrent PaO_2 to fractions of inspired oxygen ratio (FiO_2) ratio (P/F ratio) and also calculated for the first 24 hours ($WOR_{0\text{-}24}$) and over the total ICU LOS ($WOR_{ICU\ LOS}$) (13, 15).

Metrics of central tendency

The average (AVG) and median (MED) PaO_2 were calculated over the first 24 hours and over the total ICU LOS per admission.

Metrics of cumulative exposure

Per patient, the area under the curve was computed over the first 24 hours ($AUC_{0\text{-}24}$), first 96 hours ($AUC_{0\text{-}96}$) and total duration of ICU admission ($AUC_{ICU\ LOS}$) using linear interpolation of the available PaO_2 measurements. We calculated the median PaO_2 over the respective time frames and inserted these values as PaO_2 measurements at the starting (T=0) and end point of the curve (T=24, T=96 or at discharge or death, depending on considered time frame).

Smoothing curves, using natural spline interpolation (16), were fitted to compute the individual time spent in the range of hyperoxia in a similar manner. Patients with an interval longer than 24 hours between two consecutive PaO_2 measurements were excluded from these analyses (n=392), as the amount of estimated data from the fitted curve would otherwise excessively exceed the amount of real data.

Statistical Analyses

In accordance with a study examining glucose metrics in critical care (17), we analyzed the associations between the metrics and hospital mortality (primary outcome) by logistic regression with each metric categorized by severity of the hyperoxic exposure based on specified thresholds (120 and 200 mmHg) or data distribution (quintiles) and compared these categories to

normoxia (60-120 mmHg) or median quintiles. The associations between the metric and secondary outcomes, including ICU mortality, and ventilator-free days (VFDs) were also assessed. VFDs were calculated as the number of ventilator-free days and alive, 28 days after ICU admission according to a previously described definition (18).

Data were reanalyzed for specific subgroups categorized by use of mechanical ventilation, admission type and specific admission diagnoses that were studied in previous work (8, 9, 19). The multivariate models were adjusted for age and APACHE IV, which were found to be confounders in previous studies (17). The APACHE score was calculated from the data obtained within 24 hours of admission. ICU LOS was also included as potential confounder for the association with hospital mortality. In the multivariate logistic regression models, we quantify how the metrics are associated with the distribution between death and discharge at a specific time point, given that either of the two occurs (conditional hospital mortality). Adjusted associations with conditional hospital mortality were also depicted using loess smoothing curves.

The relationship between the individual metrics, that were not directly dependent on the ICU LOS, was examined using pairwise correlations and cluster analysis. The area under the receiver-operating characteristic curve (C-statistic), the Brier score and the Nagelkerke R^2 were determined as measures of discrimination and/or calibration for the univariate models of metrics using data from the first 24 hours of admission. In these models, spline based transformations of the metrics were used to predict hospital mortality. A recalibration of the APACHE IV score was explored by replacing the oxygen component by the first, mean, median, worst or highest PaO_2 within the first 24 hours of admission. The multivariate models were reanalyzed by additionally adjusting for applied FiO_2 levels and also if the oxygen component in the APACHE score covariate was removed.

All statistical analyses were conducted using R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). To account for multiple testing, the indicated levels of statistical significance were lowered to 0.01.

RESULTS

In total, 14,441 patients were included and 295,079 ABG analyses were obtained from eligible admissions (Table 1). The median time to the first ABG measurement was 26 (IQR 13-69) minutes, the median interval between two consecutive ABG samples was 249 (IQR 147-358) minutes, and the median number of ABG measurements per patient was 7 (IQR 4-17).

Metric characteristics

All metrics calculated over the first 24 hours of admission were strongly related to the corresponding metrics calculated over the total ICU LOS (Pearson r = 0.87–0.91, Supplemental Fig. 1, Supplemental Digital Content 1). Also, $AVG_{ICU\ LOS}$ had high correlation with $MED_{ICU\ LOS}$ (r = 0.92). In contrast, very low correlation (r < 0.25) was shown for $MAX_{ICU\ LOS}$ with $WOR_{ICU\ LOS}$, and $WOR_{0\text{-}24}$. Cluster analysis in the Supplemental Digital Content showed that the metrics could be subdivided in multiple families, where the highest PaO_2 appeared to be least related to the other metrics (Supplemental Fig. 2, Supplemental Digital Content 1).

Table 1. Descriptive characteristics

	Total
Patients characteristics	
No. of patients	14,441
Demographics	
Age, y	65 (55-73)
Male, n (%)	9315 (64.5)
BMI, kg/m^2	25.8 (23.3-29.0)
Planned admission, n (%)	7328 (50.7)
Medical admission, n (%)	5130 (35.5)
Planned surgery, n (%)	5038 (34.9)
Emergency surgery, n (%)	1344 (9.3)
Clinical characteristics	
APACHE IV score	54 (41-75)
APACHE IV predicted mortality, %	5.2 (1.4-22.9)
SAPS II score	34 (26-45)
SAPS II predicted mortality, %	15 (7-34)
Clinical outcomes	
Mechanical ventilation time, hrs	11 (5-40)
ICU LOS, hrs	37 (21-85)
ICU mortality, n (%)	1427 (9.9)
Hospital mortality, n (%)	1989 (13.8)
Oxygenation and ventilation characteristics	
No. of arterial blood gas analyses	295,079
Arterial blood gas results	
PaO_2, mmHg	81 (70-98)
$PaCO_2$, mmHg	40 (34-46)
pH	7.42 (7.36-7.47)
Hb, mmol/L	6.2 (1.2)
Lactate, mmol/L	1.5 (1.0-2.2)
Glucose, mmol/L	7.6 (6.4-9.1)
Ventilator settings	
FiO_2, %	40 (31-50)
PEEP, cm H_2O	7 (5-10)
Mean airway pressure, cm H_2O	11 (9-14)
Oxygenation measures	
PaO_2/FiO_2 ratio	219 (165-290)
Oxygenation index	3.8 (2.5-6.1)

Data are means (±SD) or medians (IQR), unless stated otherwise, BMI, Body Mass Index; APACHE, Acute Physiology and Chronic Health Evaluation score; SAPS, Simplified Acute Physiology Score; ICU LOS, Intensive Care Unit Length of Stay; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; Hb, hemoglobin; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure. Oxygenation index was calculated as the FiO_2/PaO_2 ratio multiplied by the concurrent mean airway pressure

Within 24 hours of admission, a spline based transformation of the worst PaO_2 was the best discriminator for hospital mortality. When recalculating the APACHE score with different metrics using PaO_2 data from the first 24 hours of admission, equal discrimination (C-statistic) was found

for APACHE IV with either worst, highest, first, average or median PaO_2 (Supplemental Table 1, Supplemental Digital Content 1).

Clinical outcomes

Unadjusted analyses showed higher mortality rates and fewer VFDs for severe hyperoxia in comparison to both mild hyperoxia and normoxia for all metrics except for the worst PaO_2, where lower or equal mortality rates and more VFDs for severe hyperoxia were assessed (Supplemental Table 2, Supplemental Digital Content 1).

Table 2 shows the event rates and adjusted estimates regarding patient-centered outcomes for each metric.

The estimates are pooled in forest plots (Supplemental Fig. 3–4, Supplemental Digital Content 1) and there were notable differences in effect size depending on the used metric for hyperoxia. The choice of a certain metric for oxygenation had major influence on the incidence of arterial hyperoxia. For example, severe hyperoxia was present in 20% of patients when using $MAX_{ICU\ LOS}$ compared to 1% of patients using $AVG_{ICU\ LOS}$.

Without exception, the point estimates for conditional mortality were larger for severe hyperoxia than for mild hyperoxia. The highest odds ratios were found for the exposure identified by the average PaO_2, closely followed by the median PaO_2. The AUC and time in arterial hyperoxia showed a consistent effect favoring the middle quintiles and no time in arterial hyperoxia. Mild hyperoxia was mainly associated with a slight increase in VFDS, whereas severe hyperoxia was associated with a decrease in VFDS. Mean PaO_2 ($AVG_{ICU\ LOS}$) showed a J-shaped relationship with hospital mortality (Figure 1).

Time spent in mild hyperoxia and time spent in severe hyperoxia both showed a linear and positive relationship with hospital mortality and were therefore also modeled linearly (Figure 2). U-shaped (FIR, $WOR_{ICU\ LOS}$, $MED_{ICU\ LOS}$) and linear ($MAX_{ICU\ LOS}$) relationships were found for the other metrics (Supplemental Fig. 5–8, Supplemental Digital Content 1).

Subpopulations

In mechanically ventilated patients, the adjusted odds ratios for conditional hospital mortality were highly comparable with the estimates for the total study population (Table 3). In large patient groups, such as planned and medical admissions, the odds ratios differed slightly from those in mechanically ventilated patients. In smaller subpopulations, including patients admitted with cardiac arrest, stroke, and sepsis, no statistically significant risks from arterial hyperoxia could be identified.

DISCUSSION

In this multicenter cohort study, we found a dose-response relationship between supraphysiological arterial oxygen levels and hospital mortality, ICU mortality and ventilator-free days. The effect size was importantly influenced by the definition of arterial hyperoxia and severe hyperoxia was more consistently associated with poor outcomes than mild hyperoxia. Furthermore, the oxygenation

Table 2. Event rates and adjusted estimates for patient-centered outcomes by metric of arterial hyperoxia

	No. of patients (%)	Deaths (%)	Hospital mortality[a] Odds Ratio [95% CI]	ICU Mortality[a] Odds Ratio [95% CI]	VFDs[b] Mean Difference [95% CI]
FIR	14441				
Mild hyperoxia[c]	4144 (29)	440 (11)	0.91 [0.79, 1.05]	0.92 [0.78, 1.09]	0.29 [-0.02, 0.59]
Severe hyperoxia[c]	1582 (11)	262 (17)	1.11 [0.92, 1.34]	1.06 [0.85, 1.31]	-0.10 [-0.54, 0.33]
$AVG_{ICU\ LOS}$	14441				
Mild hyperoxia[c]	2142 (15)	223 (10)	1.12 [0.93, 1.34]	1.35 [1.09, 1.67]*	0.32 [-0.06, 0.69]
Severe hyperoxia[c]	131 (1)	45 (34)	3.79 [2.32, 6.14]***	5.93 [3.56, 9.77]***	-3.38 [-4.81, -1.94]***
$MED_{ICU\ LOS}$	14441				
Mild hyperoxia[c]	1502 (10)	128 (9)	1.02 [0.80, 1.27]	1.12 [0.85, 1.47]	0.47 [0.04, 0.91]
Severe hyperoxia[c]	94 (1)	25 (27)	2.67 [1.42, 4.89]*	3.76 [1.93, 7.09]***	-1.50 [-3.26, 0.25]
$WOR_{ICU\ LOS}$	14062				
Mild hyperoxia[c]	1316 (9)	65 (5)	0.71 [0.52, 0.95]	0.65 [0.44, 0.93]	0.73 [0.29, 1.17]*
Severe hyperoxia[c]	86 (1)	8 (9)	1.29 [0.48, 3.05]	2.06 [0.74, 4.97]	-0.54 [-2.24, 1.16]
$MAX_{ICU\ LOS}$	14441				
Mild hyperoxia[c]	5986 (41)	745 (12)	1.07 [0.93, 1.23]	0.96 [0.81, 1.14]	-0.49 [-0.80, -0.19]*
Severe hyperoxia[c]	2854 (20)	679 (24)	1.74 [1.49, 2.03]***	1.92 [1.61, 2.30]***	-2.29 [-2.66, -1.91]***
$AUC_{ICU\ LOS}$	14049				
4^{th} quintile[d]	2810 (20)	451 (16)	1.27 [1.04, 1.54]	1.24 [0.98, 1.57]	NA
Upper quintile[d]	2810 (20)	788 (28)	1.45 [1.18, 1.78]**	1.28 [1.01, 1.63]	NA
$AVG_{0\text{-}24}$	14425				
Mild hyperoxia[c]	2896 (20)	384 (13)	1.14 [0.98, 1.32]	1.12 [0.94, 1.33]	0.02 [-0.31, 0.35]
Severe hyperoxia[c]	168 (1)	49 (29)	2.55 [1.62, 3.94]***	3.14 [1.95, 4.99]***	-1.85 [-3.10, -0.61]*
$MED_{0\text{-}24}$	14425				
Mild hyperoxia[c]	2090 (14)	237 (11)	1.10 [0.92, 1.31]	1.09 [0.88, 1.34]	0.16 [-0.21, 0.54]
Severe hyperoxia[c]	122 (1)	31 (25)	2.49 [1.44, 4.20]**	2.60 [1.42, 4.61]*	-1.27 [-2.78, 0.23]
$WOR_{0\text{-}24}$	14046				
Mild hyperoxia[c]	1556 (11)	122 (8)	1.01 [0.80, 1.26]	0.98 [0.74, 1.28]	0.50 [0.09, 0.91]
Severe hyperoxia[c]	104 (1)	12 (12)	1.75 [0.79, 3.57]	2.37 [1.02, 5.02]	-0.85 [-2.39, 0.70]

Table 2. (continued)

	No. of patients (%)	Deaths (%)	Hospital mortality[a] Odds Ratio [95% CI]	ICU Mortality[a] Odds Ratio [95% CI]	VFDs[b] Mean Difference [95% CI]
MAX_{0-24}	14425				
Mild hyperoxia[c]	5617 (39)	674 (12)	0.89 [0.78, 1.02]	0.87 [0.74, 1.02]	0.33 [0.03, 0.62]
Severe hyperoxia[c]	2384 (17)	482 (20)	1.23 [1.05, 1.44]*	1.29 [1.08, 1.54]*	-0.39 [-0.78, -0.01]
AUC_{0-24}	8646				
4th quintile[d]	1729 (20)	316 (18)	0.99 [0.81, 1.21]	0.97 [0.77, 1.22]	-0.04 [-0.68, 0.60]
Upper quintile[d]	1729 (20)	359 (21)	1.29 [1.06, 1.57]	1.30 [1.04, 1.63]	-0.45 [-1.09, 0.18]
AUC_{0-96}	3083				
4th quintile[d]	616 (20)	170 (28)	1.20 [0.92, 1.57]	1.07 [0.79, 1.43]	NA
Upper quintile[d]	617 (20)	185 (30)	1.45 [1.11, 1.90]*	1.13 [0.84, 1.53]	NA
Time in mild hyperoxia					
Upper quintile[e]	2810 (20)	584 (21)	1.25 [1.06, 1.50]*	1.10 [0.89, 1.35]	NA
Time in severe hyperoxia					
Upper quintile[f]	2810 (20)	415 (16)	1.31 [1.12, 1.53]**	1.66 [1.39, 1.99]***	NA

FIR, first PaO_2; AVG, mean PaO_2; MED, median PaO_2; WOR, worst PaO_2; MAX, highest PaO_2; AUC, Area Under Curve of PaO_2 measurements in considered time frame. VFDs, ventilator-free days and alive at day 28;

Metrics are calculated over the total ICU length of stay (ICU LOS), over the first 24 hours of ICU admission (0-24) or over the first 96 hours of admission (0-96), as indicated.

Some patients were excluded for specific metric analyses if there was no requisite data within the first 24 hours of admission (0-24 subgroups), if there was no data on PaO_2/FiO_2 ratio (WOR) or if there was an interval longer than 24 hours between two consecutive PaO_2 measurements (AUC and time spent in hyperoxia).

* P<0.01; ** P<0.001; *** P<0.0001. NA, not applicable according to used model

Mild hyperoxia, PaO_2 120-200 mmHg; severe hyperoxia, PaO_2 >200 mmHg

[a] Model is adjusted for age, APACHE IV score, and ICU LOS.

Hospital and ICU mortality refer to mortality, given either death or discharge (conditional hospital mortality)

[b] Subgroup analyses on mechanically ventilated patients. Model is adjusted for age and APACHE IV score

[c] Arterial normoxia (PaO_2 60-120 mmHg) used as reference range

[d] Middle quintile (AUC) used as reference range

[e] Zero time in mild hyperoxia is used as reference range. Upper quintile is ≥ 470 minutes

[f] Zero time in severe hyperoxia is used as reference range. Upper quintile is ≥200 minutes

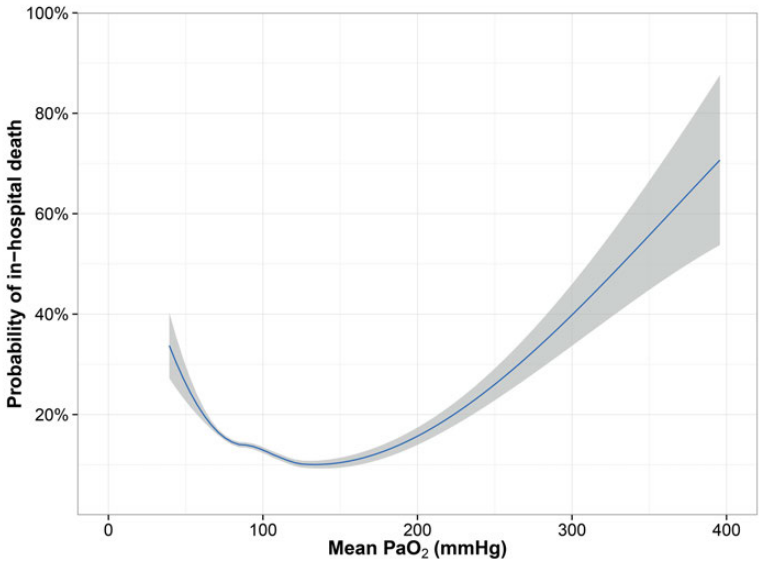

Figure 1. Adjusted probability of in-hospital death by mean PaO_2.
Loess smoothing curve predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Blue line represents oxygenation by mean PaO_2 over the total ICU LOS. Grey zones represent 95% confidence intervals.

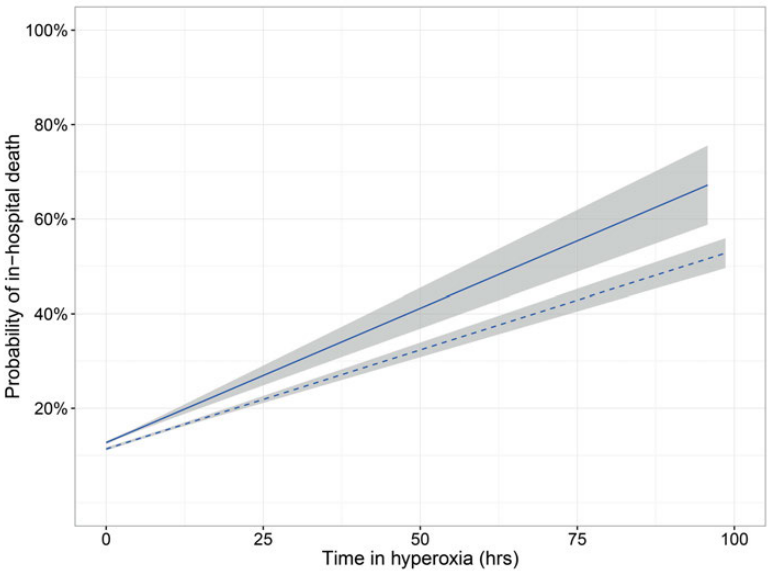

Figure 2. Adjusted probability of in-hospital death by time in hyperoxia.
Probability of death predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Lines represent estimated time in mild (dashed) and severe (solid) hyperoxia. Grey zones represent 95% confidence intervals. A linear model was presented, because the smoothing curve for both metrics showed a clear linear relationship between the predicted outcome and time in hyperoxia.

Table 3. Arterial hyperoxia and adjusted odds ratios (95%CI) for hospital mortality by subpopulation

	Mechanical ventilation	Planned admission	Medical admission	Cardiac arrest	Stroke	Sepsis
No. of patients (%)	11934 (82.6)	7328 (50.7)	5130 (35.5)	673 (4.7)	406 (2.8)	548 (3.9)
Deaths (%)	1746 (14.6)	241 (3.3)	1410 (27.5)	316 (47.0)	146 (36.0)	183 (33.4)
FIR						
Mild hyperoxia[a]	0.91 [0.78, 1.06]	0.95 [0.67, 1.32]	0.97 [0.80, 1.16]	1.27 [0.84, 1.91]	1.00 [0.57, 1.74]	1.18 [0.65, 2.11]
Severe hyperoxia[a]	1.14 [0.94, 1.39]	1.33 [0.81, 2.12]	1.06 [0.84, 1.35]	1.41 [0.88, 2.29]	0.61 [0.27, 1.32]	0.97 [0.40, 2.32]
AVG						
Mild hyperoxia[a]	1.11 [0.91, 1.35]	1.38 [0.89, 2.08]	1.17 [0.90, 1.50]	1.41 [0.80, 2.51]	0.98 [0.50, 1.90]	1.35 [0.57, 3.14]
Severe hyperoxia[a]	4.11 [2.42, 6.90]***	1.74 [0.10, 9.41]	4.00 [2.16, 7.48]***	3.24 [0.84, 16.57]	3.85 [0.91, 19.11]	NA
MED						
Mild hyperoxia[a]	0.99 [0.77, 1.26]	1.14 [0.63, 1.91]	1.15 [0.83, 1.57]	1.25 [0.59, 2.63]	0.89 [0.42, 1.83]	1.60 [0.51, 4.53]
Severe hyperoxia[a]	2.41 [1.19, 4.74]	3.11 [0.17, 16.99]	2.34 [1.07, 4.98]	2.33 [0.54, 12.58]	0.39 [0.01, 5.41]	NA
WOR						
Mild hyperoxia[a]	0.63 [0.46, 0.85]*	0.73 [0.33, 1.44]	0.71 [0.44, 1.10]	0.98 [0.40, 2.37]	0.77 [0.26, 2.12]	2.73 [0.37, 15.12]
Severe hyperoxia[a]	1.20 [0.44, 2.88]	2.68 [0.15, 13.12]	1.14 [0.29, 3.85]	0.86 [0.10, 6.29]	NA	NA
MAX						
Mild hyperoxia[a]	1.08 [0.93, 1.27]	0.93 [0.65, 1.33]	1.16 [0.98, 1.38]	1.10 [0.71, 1.71]	0.92 [0.49, 1.72]	1.00 [0.61, 1.61]
Severe hyperoxia[a]	1.82 [1.54, 2.16]***	2.10 [1.44, 3.06]**	1.78 [1.47, 2.17]***	2.14 [1.32, 3.49]*	0.96 [0.49, 1.91]	1.03 [0.55, 1.93]
Time in mild hyperoxia						
Upper quintile[c]	1.36 [1.14, 1.63]**	1.52 [0.99, 2.34]	1.35 [1.11, 1.64]*	1.45 [0.88, 2.39]	0.66 [0.32, 1.35]	1.18 [0.65, 2.14]
Time in severe hyperoxia						
Upper quintile[d]	1.36 [1.15, 1.61]**	1.75 [1.21, 2.52]*	1.57 [1.28, 1.94]***	1.59 [0.98, 2.58]	0.68 [0.36, 1.25]	0.71 [0.35, 1.40]

FIR, first PaO_2; AVG, mean PaO_2; MED, median PaO_2; WOR, worst PaO_2; MAX, highest PaO_2. All shown metrics are calculated over the total ICU length of stay. * P<0.01; ** P<0.001; *** P<0.0001. NA, not available (not enough patients in specific subset). Mild hyperoxia, PaO_2 120-200 mmHg; severe hyperoxia, PaO_2 >200 mmHg. Models are adjusted for age, APACHE IV score, and ICU LOS. Hospital mortality refers to mortality, given either death or discharge (conditional hospital mortality). [a] Normoxia (PaO_2 60-120 mmHg) used as reference range. [b] Middle quintile (AUC) used as reference range. [c] Zero time in mild hyperoxia is used as reference range. [d] Zero time in severe hyperoxia is used as reference range

metric that defines the exposure was shown to be an essential factor in determining the risk for the studied population.

We selected a variety of metrics that were identified by a previous systematic review of the literature (9). These pre-existing metrics are usually calculated over the first 24 hours of admission, but our findings show that exposure to arterial hyperoxia in other time frames and using different definitions may substantially impact on the studied outcomes. For this study a new set of relevant oxygenation metrics was compiled for ICU patients. This allowed for comprehensive insights in the epidemiology and associated outcomes across multiple abstractions of arterial hyperoxia. However, we cannot rule out that the observed effects in this study can be subtly altered when alternative metrics are used.

By studying the continuous application-related adverse effects of hyperoxia this study addressed the timely clinical questions whether arterial hyperoxia is a biomarker for mortality and when the exposure is sufficient to cause harm (20-22). Metrics of central tendency (mean, median) were found to have the strongest relationship with outcome. The effects were smaller for the metrics of single measurements (i.e. highest, worst, first). In this context, the maximum PaO_2 value may be an incidental outlier but could also be indicative of a longer lasting, gradual process of increasing PaO_2 levels where a maximum is ultimately achieved, thereby mimicking metrics of central tendency. However, the latter explanation is less likely as this metric was shown to substantially differ from other metrics in cluster, correlation, and regression analyses.

Metrics of cumulative oxygen exposure, including hourly exposure and AUC in the first 24 hours, have recently been used by Elmer et al. to show associations with morbidity and mortality after cardiac arrest (23, 24). We additionally calculated AUC and time in arterial hyperoxia from admission to discharge, which may be a more accurate measure of total hyperoxia exposure even though exposure beyond the ICU admission, e.g. in the general wards, was not considered in this study. Assuming that these metrics closely reflect the actual exposure, the association between arterial hyperoxia and poor outcome is consistent in multivariate models which account for the total length of stay and illness severity. Notably, our results were essentially unchanged when the multivariate models were additionally adjusted for applied FiO_2 levels and also if the oxygen component in the APACHE score covariate was removed in order to avoid overadjustment. Still, we cannot exclude that residual confounding may be present from unmeasured variables.

In contrast with a previous study in mechanically ventilated patients (13) but in concordance with another (15), hyperoxia identified by the worst PaO_2 in the first 24 hours was not significantly associated with hospital mortality. Since the spline based transformation of this metric calculated over the total ICU LOS did emerge as the best discriminator for mortality, the association may be primarily driven by the discriminative capability of the arterial normoxia and/or hypoxia range. In other words, the worst PaO_2 is an important measure over the total ICU stay, but within the first 24 hours a hypoxic worst PaO_2 may predict mortality more precise than a hyperoxic measurement. When comparing previous studies, the selected metrics should be explicitly considered, as we showed that this may considerably impact on the observed effect sizes. Regional differences in oxygen management and cohort type may further be responsible for specific study differences. For careful interpretation of the outcome, the sample size and event rates in the studied oxygenation

ranges by different metrics should also be taken into consideration. Indeed, the probability of type 2 errors increases with relatively low numbers of exposed patients in specific subsets. In smaller subsets of cardiac arrest, stroke, or sepsis patients, our risk estimates were in the same order of magnitude as previously found for arterial hyperoxia although subtle differences can be designated (7, 9, 25-27). The absence of significant effects in small subsets may be a signal of the used definition or may reflect indifferent outcome or a lack of statistical power. Analyses in different subpopulations should therefore mainly be considered exploratory and interpreted with caution. Also, we accounted for multiple testing by lowering the level for statistical significance.

Several limitations deserve further mention. First, methodological flaws following the retrospective nature of this study should be considered and causality cannot be inferred. Second, immortal time bias may play a role in models predicting hazard when no censored data is available. We therefore corrected for the total ICU LOS in multivariate analyses, modeled hospital mortality given either death or discharge, and only analyzed the predictive value for metrics that were not computed based on the total ICU LOS. The inherent limitation of non-continuous PaO_2 sampling with a lack of data between successive measurements was overcome by using linear and natural spline interpolation between separate PaO_2 measurements and calculate area under the curves and time spent in arterial hyperoxia, but it should be considered that real data of unmeasured arterial oxygenation and ventilatory management was not available. Further, our statistical models were fully calibrated on the data of the present cohort but may not universally fit other data and cannot be directly extrapolated to other cohorts. We used a cohort in which conservative oxygenation was promoted, and the exposure rates may therefore differ in comparison to other hospitals. However, we used a multicenter cohort and the concepts are likely to be comparable across different ICUs and regions. Indeed, our findings were quite consistent in the three participating centers and over time. The dose-response relationship was recently also illustrated in a meta-regression of cohort studies (9). When pooling these studies, heterogeneity of included studies was found to be substantial, which could be partially explained by the use of different metrics for arterial hyperoxia and different multivariate models.

Strengths of our study include the representation of arterial hyperoxia by several relevant and novel analytical metrics of PaO_2, the large multicenter cohort and an unprecedented set of ABG samples, including data within and beyond the first 24 hours of admission. We placed previously found associations of arterial hyperoxia with hospital mortality in a broader and clinically relevant context of varying definitions, durations and also included secondary outcomes, such as length of stay, mechanical ventilation time and ventilator-free days. Our strategies to investigate the effects of a continuously changing parameter on patient-centered outcomes can be further applied as a toolbox for other clinical challenges such as glucose and carbon dioxide management.

The present findings underline the importance of preventing excessive oxygenation during prolonged periods and urge careful oxygen titration in critically ill and mechanically ventilated patients. PaO_2 levels exceeding 200 mmHg were not only associated with ICU mortality and hospital mortality but may also lead to fewer ventilator-free days. Mild hyperoxia was not consistently shown to be harmful and may have beneficial properties when attempting to compensate and prevent impaired oxygen delivery. Interestingly, however, our analyses show that the probability

of death increases linearly when the exposure time in mild hyperoxia increases strongly. Thus, on the short term mild hyperoxia may not directly impact on outcome, but clinicians should still be aware that cumulative exposure to even mild hyperoxia may be harmful. Taking this into account, exposure time may also be a marker of responsive care, even though the effect sizes were similar when adjusting for proxy markers of less responsive care (e.g. lowest glucose). It should be realized that hyperoxia is a label that admits to several definitions, where PaO_2 is not a single indicator of blood oxygen and may embrace both care given and the consequences of that care. The curvilinear relationship between the metrics and outcome, suggest that both arterial hypoxia and arterial hyperoxia should be actively avoided, and deviations from the normal may be a result of unfavorable oxygen management. Given the diversity of patients, clinical scenarios and characteristics of oxygen, universal recommendations remain cumbersome. However, in expectation of future randomized controlled trials, our findings may be auxiliary to guide targeted oxygen management by estimating the potential risk in different clinical situations.

CONCLUSIONS

We found that metrics of central tendency for severe arterial hyperoxia, as well as exposure time for mild and severe arterial hyperoxia, were associated with unfavorable outcomes of ICU patients and this association was found both within and beyond the first day of admission. Our results suggest that the relationship was consistent for large patient groups and that previously used approaches may not have completely captured the actual exposure effects.

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ONLINE SUPPLEMENT

For the online supplement, please use the following weblink, or scan the QR-code with your mobile device

Supplemental Table 1 – 2; Supplemental Fig. 1 – 8, Supplemental Digital Content 1: http://links.lww.com/CCM/C113

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Part III

OXYGEN MANAGEMENT AND PREVENTIVE STRATEGIES

8

SELF-REPORTED ATTITUDES VERSUS ACTUAL PRACTICE OF OXYGEN THERAPY BY ICU PHYSICIANS AND NURSES

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ABSTRACT

Background

High inspiratory oxygen concentrations are frequently administered in ventilated patients in the intensive care unit (ICU) but may induce lung injury and systemic toxicity. We compared beliefs and actual clinical practice regarding oxygen therapy in critically ill patients.

Methods

In three large teaching hospitals in the Netherlands, ICU physicians and nurses were invited to complete a questionnaire about oxygen therapy. Furthermore, arterial blood gas (ABG) analysis data and ventilator settings were retrieved to assess actual oxygen practice in the same hospitals 1 year prior to the survey.

Results

In total, 59% of the 215 respondents believed that oxygen-induced lung injury is a concern. The majority of physicians and nurses stated that minimal acceptable oxygen saturation and partial arterial oxygen pressure (PaO_2) ranges were 85% to 95% and 7 to 10 kPa (52.5 to 75 mmHg), respectively. Analysis of 107,888 ABG results with concurrent ventilator settings, derived from 5,565 patient admissions, showed a median (interquartile range (IQR)) PaO_2 of 11.7 kPa (9.9 to 14.3) [87.8 mmHg], median fractions of inspired oxygen (FiO_2) of 0.4 (0.4 to 0.5), and median positive end-expiratory pressure (PEEP) of 5 (5 to 8) cm H_2O. Of all PaO_2 values, 73% were higher than the upper limit of the commonly self-reported acceptable range, and in 58% of these cases, neither FiO_2 nor PEEP levels were lowered until the next ABG sample was taken.

Conclusions

Most ICU clinicians acknowledge the potential adverse effects of prolonged exposure to hyperoxia and report a low tolerance for high oxygen levels. However, in actual clinical practice, a large proportion of their ICU patients was exposed to higher arterial oxygen levels than self-reported target ranges.

BACKGROUND

Oxygen supply during mechanical ventilation is a highly effective and uniformly used intervention to support oxygenation of mechanically ventilated patients in the intensive care unit (ICU). Although oxygen administration is a lifesaving strategy in the management of patients with respiratory insufficiency, the clinical implications of hyperoxia remain an important subject of debate (1). The controversies are triggered by a considerable number of studies showing both beneficial, harmful and/or insignificant effects of oxygen therapy on outcome in different subgroups (2-15). However, morbidity and mortality may be substantially impacted by the used threshold and depend on degree, duration, and susceptibility for hyperoxia.

The emerging laboratory evidence for the double-edged nature of oxygen (lifesaving but also potentially harmful) is compelling (16-22), but robust clinical studies and evidence-based guidelines in critically ill patients are still limited (23-26). Consequently, the attitudes and beliefs in the management of oxygen administration vary considerably in clinical practice (27, 28). In general, physicians are inclined to treat hypoxemia aggressively in order to achieve satisfactory tissue oxygenation (23, 29, 30). However, hyperoxemia is often considered acceptable, especially when applied fractions of inspired oxygen (FiO_2) are relatively low (31-33).

Given the lack of established guidelines on oxygen therapy in ICU patients, our study was designed to investigate the common beliefs and self-reported attitudes of ICU physicians and nurses on oxygenation targets and to compare this with actual treatment of ICU patients in the same hospitals. We hypothesized that the potential harmful effects of oxygen are well known and generally acknowledged, but that in real clinical practice, hyperoxia is not a major concern for ICU professionals.

METHODS

Questionnaire

An anonymous online survey was performed between June and August 2012 to elicit the self-reported behavior of ICU personnel with respect to oxygen therapy. The questionnaire was a modified and comprehensive version of previously used questionnaires from Canada and Australia/New Zealand (27, 28) and comprised multiple choice questions (see Additional file 1). The target population consisted of physicians and nurses, working in closed format, mixed medical and surgical, tertiary care ICUs of three participating hospitals, including two academic and one large teaching hospital in the Netherlands. Participants were invited by email to complete the online questionnaire. A reminder was sent once to all participants.

Patient data

Analyses were performed on data recorded between 1 April 2011 and 31 March 2012 for all patients admitted to the ICU departments of the same hospitals that participated in the questionnaire study. Anonymous encrypted data were collected from the patient data management system (PDMS) database (MetaVision, iMDsoft, Leiden, The Netherlands). According to the Dutch Medical Research Involving Human Subjects Act, there was no need for informed patient consent or approval by ethical committees, as only registries without patient identifying information were used.

Arterial blood gas (ABG) analyses and concurrent ventilator settings were extracted to retrospectively assess actual practices regarding oxygen therapy. Data from ICU admission to dismissal or death were included for analysis. Data with a partial arterial oxygen pressure (PaO_2) of ≤4.5 kPa or 33.8 mmHg (n=209) were excluded to prevent confounding by venous blood gas samples. Further exclusion of samples with PaO_2 of 4.5 to 5.0 kPa (n=146) or PaO_2 of 5.0 to 6.0 kPa (n=356) did not materially change our observations (data not shown). Every set of ABG data and ventilator settings was compared with the following set, as described previously (32). Prone positioning, recruitment maneuvers, and other efforts that may improve oxygenation could not be explored in this database. Clinicians' responses to ABG results were explored by analyzing the FiO_2 and positive end-expiratory pressure (PEEP) adjustments in a subsample of mechanically ventilated patients when more than two ABG samples and ventilator settings were recorded. PaO_2 values were categorized according to the commonly self-reported acceptable range (7 to 10 kPa or 52.5 to 75 mmHg) extracted from the survey results (Fig. 1). This range is roughly consistent with oxygenation goals (7.3 to 10.7 kPa or 55 to 80 mmHg) previously suggested by the Acute Respiratory Distress Syndrome (ARDS) network (30, 34).

Mechanical ventilation protocol

Local guidelines, applicable during the survey and collection of ABG and ventilation data, instructed for lowest acceptable FiO_2 levels. FiO_2 levels higher than 60% should be avoided by increasing PEEP levels, instituting inverse-ratio ventilation or prone positioning. No explicit target ranges for PaO_2, FiO_2, or saturation were specified in the participating hospitals during this period.

Statistical analysis

All data are expressed as percentages of the total number of respondents for the particular questions, unless otherwise specified. Data are presented as means (±SD) or medians (interquartile range, IQR) depending on data distributions, unless stated otherwise. For assessing differences between physicians and nurses, ICU personnel were grouped according to their respective profession and data were analyzed using Fisher's exact tests. ICU physicians, fellows, and residents were classified as physicians; ICU nurses and ICU nurses in training were classified as nurses.

Statistical analyses were conducted using STATA/SE 10.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Data derived from questionnaire

Respondent characteristics

Approximately 500 potential participants were invited to complete the online questionnaire. Full or partial responses were received from 215 ICU physicians and nurses with a mean age of 40.4±10.0 years (range 24 to 62). In total, 171 (80%) respondents fully completed all questions. The group of respondents consisted of 28 (13%) critical care physicians, 15 (7%) fellows, 15 (7%) residents, 141 (66%) ICU nurses, 11 (5%) ICU nurses in training, and 5 (2%) ICU clinicians with another type of practice.

Opinions towards oxygen toxicity

The responses are listed in Table 1. Overall, 126 (59%) respondents considered oxygen induced lung injury in mechanically ventilated patients a major concern. However, the vast majority of respondents (81%) considered high tidal volumes and high inspiratory pressures as the greatest risk for lung injury in mechanically ventilated patients. No differences between physicians and nurses were detected.

Self-reported acceptance of hyperoxemia and hypoxemia

The percentages of respondents accepting various oxygenation ranges in a young to middle-aged mechanically ventilated patient with ARDS are shown in Figure 1.

For both short and longer lasting periods, the vast majority of respondents choose 7 to 10 kPa (52.5 to 75 mmHg) as the lowest acceptable PaO_2 range. Physicians were more tolerant towards lower PaO_2 limits for short duration than nurses (P<0.001).

Table 1. Questionnaire responses regarding risks assessment and management in oxygen therapy

Question	Responses (% of total)	Physicians vs. nurses
Is oxygen induced lung injury a concern when placing a patient on mechanical ventilation?		NS
YES, a major concern	126 (59%)	
due to the *high incidence* of injury	13 (6%)	
due to the *severity* of injury	63 (29%)	
due to the *high incidence and severity* of injury	50 (23%)	
YES, but not a *major* concern	80 (37%)	
NO, it is not a concern	9 (4%)	
In your opinion, which one of the following two situations poses a greater threat of lung injury for mechanically ventilated patients?		NS
High FiO_2	35 (16%)	
High tidal volumes and high ventilator pressures	173 (81%)	
Don't know	7 (3%)	
In situations when maximal SaO_2 achievable is low (±85%) or when FiO_2 requirements are high, do you assess indices of tissue oxygenation?		P=0.05
NO	91 (43%)	
YES, lactate	88 (42%)	
YES, microcirculation with OPS/SDF imaging	4 (2%)	
YES, a combination of indices	20 (9%)	
YES, SvO_2	6 (3%)	
YES, other	2 (1%)	

NS, Not significant; FiO_2, Fractions of inspired Oxygen; OPS, Orthogonal Polarization Spectral; SDF, Sidestream Dark Field; SaO_2, Arterial Oxygen Saturation; SvO_2, Mixed Venous Oxygen Saturation

Presented with a patient whose arterial oxygen saturation (SaO_2) levels are low (<85%) or FiO_2 requirements are high, indices of tissue oxygenation were frequently assessed (Table 1). Differences between physicians and nurses approached statistical significance (P=0.05), with physicians favoring lactate assessment, and nurses being less likely to demand some assessment of tissue oxygenation. Nurses in training more often favored lactate assessment than senior ICU nurses (P=0.01).

Adjustment of FiO_2 in specific clinical cases

The proportions of ICU clinicians adjusting FiO_2 levels in specified clinical cases are listed in Table 2. Observed differences by profession were mainly restricted to questions regarding patients with untreatable anemia, where physicians generally favored higher FiO_2 levels than nurses. Only minor differences within the clustered categories of physicians (comparison between physicians, fellows, residents) and nurses (ICU nurses, nurses in training) were observed.

Data derived from ABG measurements and ventilator settings

Descriptive data

A total of 107,888 ABG results with concurrent ventilator settings, covering 5,565 patient admissions, were retrieved and included for analysis over a 1-year period prior to the survey in three hospitals. Median interval between two consecutive ABG samples was 214 min (IQR 130 to 331), and the median number of ABG samples per patient was 7 (IQR 4 to 19). Mean PaO_2 was 12.9 kPa (SD 5.1) or 96.8 mmHg and median PaO_2 was 11.7 kPa (IQR 9.9 to 14.3) or 87.8 mmHg. Overall, in 25.3% of ABG results, PaO_2 was in the self-reported range (7 to 10 kPa), 1.2% was lower and 73.4% was higher than the predefined range.

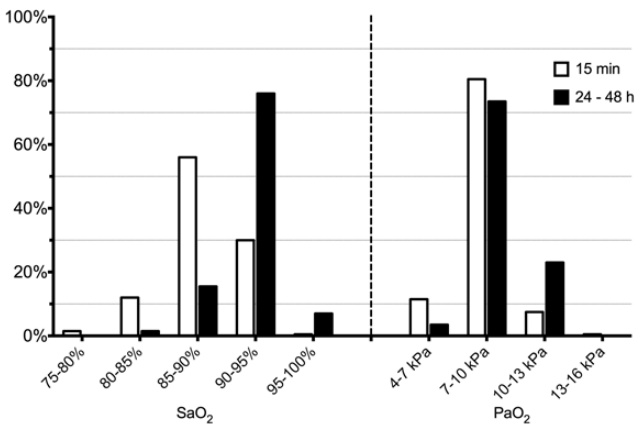

Figure 1. Self-reported tolerance limits for short-term (15 min, open bars) and longer term (24 to 48 h, closed bars) oxygenation.
Bars represent percentage of respondents (n=200). The presented case is a young to middle-aged ARDS patient in the ICU requiring mechanical ventilation. Ventilator settings (e.g., PEEP, airway pressures, I:E ratio, flow ratio) are optimized with respect to the PaO_2/FiO_2 ratio and hemodynamic indices. Lung injury due to high FiO_2 and/or ventilator settings is minimized. There is no evidence to indicate end-organ ischemia, and hemodynamics are stable.

Table 2. Percentages of respondents adjusting FiO2 levels in specified clinical conditions with presented levels of arterial oxygenation

Clinical condition	ARDS			Cardiac ischemia			Cerebral ischemia			Sepsis			Untreatable anemia		
FiO_2 response	Higher	Unchanged	Lower	Higher	Unchanged	Lower	Higher	Unchanged	Lower	Higher	Unchanged	Lower	Higher	Unchanged	Lower
SaO_2															
80-85%	97.4	2.6	0.0	100	0.0	0.0	98.9	1.1	0.0	99.5	0.5	0.0	92.4	7.1	0.5
85-90%	61.5	38.5	0.0	96.4	3.6	0.0	91.4	8.0	0.5	92.5	7.0	0.5	85.3	13.6	1.1
90-95%	4.1	78.5	17.4	42.6	54.9	2.6	23.0	71.7	5.3	19.3	75.9	4.8	57.6	36.4	6.0
95-100%	0.0	17.4	82.6	2.6	61.0	36.4	0.5	41.2	58.3	0.5	40.1	59.4	13.6	58.7	27.7
PaO_2															
6 kPa	96.6	3.4	0.0	98.3	1.7	0.0	98.3	1.7	0.0	98.3	1.7	0.0	96.5	3.5	0.0
9 kPa	9.0	85.3	5.6	60.1	38.2	1.7	40.6	58.9	0.6	37.7	60.6	1.7	66.7	31.6	1.8
12 kPa	0.6	27.1	72.3	5.6	60.7	33.7	2.3	53.7	44.0	2.9	47.4	49.7	22.2	52.6	25.1
16 kPa	0.0	2.3	97.7	2.2	10.1	87.6	1.1	4.6	94.3	0.6	7.4	92.0	6.4	25.7	67.8

All clinical situations represent patients in the ICU, who have been invasively mechanically ventilated for at least 5 days, with FiO_2 set at 50%. ARDS, patient with acute respiratory distress syndrome and pneumonia; Cardiac ischemia, patient with signs of cardiac ischemia (ST-depressions in the anterior leads [max 3 mm]) and pneumonia; Cerebral ischemia, patient with recent cerebral ischemia and one-sided hemiplegia; Sepsis, patient with a liver abscess and sepsis; Untreatable anemia, Jehovah's Witness with stable hemoglobin of 1.8 mmol/L after gastric bleeding. Higher, i.e. increase FiO_2, higher than current 50%; Unchanged, i.e. maintain FiO_2 at current 50%; Lower, i.e. decrease FiO_2, lower than current 50%

Mechanical ventilation settings showed a mean PEEP of 6.1 cm H_2O (SD 4.3), and median PEEP was 5 (IQR 5 to 8). Mean FiO_2 was 0.45 (SD 0.14), and median FiO_2 was 0.40 (IQR 0.40 to 0.50). Only small differences were observed between the three participating hospitals.

Recorded FiO_2 adjustments following ABG analysis

After exclusion of spontaneously breathing and non-invasively ventilated patients, 62,875 ABG records derived from 4,264 mechanically ventilated patients were included for analysis of FiO_2 adjustments in response to ABG samples.

Analyzing every first registered ABG sample in the ICU, 62,222 PaO_2 measurements covering 3,791 patients were retrospectively categorized in predefined ranges and were followed by a recorded FiO_2 adjustment. The subsequently registered PaO_2 measurement was compared with the first registered PaO_2 (Table 3).

Table 4 shows that quantity, direction, and magnitude of ventilator adjustments in response to high arterial oxygen levels are considerably influenced by the level of FiO_2. In 58.3% of cases with PaO_2 higher than the upper level of the commonly self-reported acceptable oxygenation (10 kPa or 75 mmHg), neither FiO_2 nor PEEP levels had been lowered when the next ABG sample was taken.

Table 3. FiO_2 adjustment following ABG analysis and its effects on oxygenation measured in the next ABG

		Successive PaO_2 [n=61,073]		
PaO_2 (%) [n=107,888]	**Adjustment of FiO_2 (%) [n=62,222]**	**Higher (Delta PaO_2)**	**Unchanged**	**Lower (Delta PaO_2)**
<7 kPa (1.2)	Higher (34.7)	96.6% (+5.3)	0.4%	3.0% (-0.5)
	Unchanged (46.9)	87.4% (+5.6)	3.2%	9.4% (-0.6)
	Lower (18.4)	95.1% (+7.9)	2.4%	2.5% (-0.9)
7–10 kPa (25.3)	Higher (27.9)	76.3% (+3.1)	2.7%	21.0% (-0.9)
	Unchanged (56.0)	66.3% (+2.0)	4.3%	29.4% (-0.8)
	Lower (16.1)	61.3% (+2.6)	3.6%	35.1% (-1.0)
>10 kPa (73.4)	Higher (10.8)	48.6% (+4.6)	2.1%	49.3% (-3.1)
	Unchanged (62.0)	44.7% (+2.1)	3.1%	52.2% (-2.3)
	Lower (27.2)	23.5% (+2.4)	1.7%	74.8% (-4.6)
Total (100)	–	46.3% (+2.6)	2.7%	51.0% (-2.9)

Data presented as percentages of total and irrespective of adjustment of other ventilator settings (e.g. PEEP, I:E ratio). Delta, mean difference between two successive ABG samples; PaO_2, any recorderd PaO_2 stratified by self-reported ranges; Successive PaO_2, PaO_2 from successively registered ABG sample; Higher, i.e. increased FiO_2 (column 2) or PaO_2 (column 3), higher than previous level; Unchanged, i.e. FiO_2 or PaO_2 equal to previous level; Lower, i.e. decreased FiO_2 or PaO_2, lower than previous level. A total of 62,222 PaO_2 measurements from 3,791 patients (57.7% of all 107,888 ABG samples) in the database is followed by an adjustment of ventilator settings, and 98.2% of PO_2 measurements is followed by a successive PO_2 measurement (n=61,073) in the same patient when adjustment of FiO_2 is also measured.

Table 4. Adjustment of mechanical ventilation settings following ABG analysis,

	FiO_2 25-40% (n=37,172)			FiO_2 40-60% (n=23,466)			FiO_2 60-80% (n=4,318)			FiO_2 80-100% (n=2,041)			**Total** (n=68,222)		
PaO_2	13.4 (4.1)			12.6 (5.2)			12.3 (6.6)			16.0 (13.7)			13.1 (5.2)		
SpO_2	98.0 (2.9)			96.5 (3.8)			94.3 (6.3)			89.7 (12.5)			96.9 (4.6)		
PEEP	5.6 (3.4)			7.3 (4.4)			9.1 (5.6)			9.0 (6.3)			6.5 (4.2)		
PaO_2 range (kPa)	Delta FiO_2 (%)	Delta PEEP (cm H_2O)	No decrease in FiO_2 or PEEP (%)	Delta FiO_2 (%)	Delta PEEP (cm H_2O)	No decrease in FiO_2 or PEEP (%)	Delta FiO_2 (%)	Delta PEEP (cm H_2O)	No decrease in FiO_2 or PEEP (%)	Delta FiO_2 (%)	Delta PEEP (cm H_2O)	No decrease in FiO_2 or PEEP (%)	Delta FiO_2 (%)	Delta PEEP (cm H_2O)	No decrease in FiO_2 or PEEP (%)
<7	+6.1 (13.8)	+0.3 (3.2)	87.6	+5.4 (13.2)	+0.7 (3.7)	81.3	+2.0 (14.5)	+0.6 (6.0)	86.3	-7.0 (16.8)	+1.0 (6.7)	76.9	+3.0 (14.8)	+0.7 (4.3)	83.3
7-10	+2.6 (6.7)	+0.1 (3.1)	81.9	+1.6 (7.3)	+0.2 (4.0)	80.3	-0.2 (9.4)	+0.3 (5.2)	80.8	-6.7 (14.8)	+0.1 (5.9)	76.5	+1.3 (8.3)	+0.2 (3.8)	80.8
10-15	+0.6 (4.9)	-0.2 (2.7)	72.9	-1.5 (6.6)	-0.2 (3.8)	48.2	-5.2 (9.2)	+0.1 (4.9)	33.7	-15.6 (19.2)	+0.4 (5.7)	31.1	-0.6 (6.7)	-0.1 (3.2)	62.3
15-20	-0.3 (5.1)	-0.3 (2.7)	65.0	-4.8 (7.2)	-0.3 (3.3)	25.1	-11.2 (11.4)	+0.1 (4.7)	13.5	-20.4 (20.5)	+0.0 (4.7)	23.6	-2.0 (7.3)	-0.2 (3.0)	52.8
20-25	-1.2 (6.4)	-0.2 (2.4)	54.2	-6.1 (9.0)	-0.4 (3.0)	22.1	-12.7 (12.4)	-0.4 (5.3)	11.8	-25.9 (21.7)	-0.1 (4.8)	21.3	-4.2 (10.1)	-0.3 (2.9)	40.4
25-30	-1.6 (7.0)	-0.4 (2.8)	51.6	-7.2 (9.6)	-0.3 (2.7)	18.8	-19.0 (12.1)	-0.4 (3.8)	9.2	-25.3 (21.6)	-0.1 (4.8)	22.9	-7.1 (12.2)	-0.3 (2.9)	32.0
>30	-1.0 (6.6)	-0.4 (4.0)	69.8	-3.5 (9.6)	-0.4 (4.5)	43.0	-15.4 (15.8)	+0.3 (5.7)	24.8	-33.6 (23.2)	-0.4 (4.0)	14.3	-5.7 (15.9)	-0.3 (4.2)	51.6

Data are means (±SD), unless stated otherwise. Delta, difference between two successive ABG samples

DISCUSSION

In accordance with accumulating laboratory evidence for the toxic effects of oxygen in pulmonary injury (1, 35-38), the majority of surveyed ICU physicians and nurses consider prolonged hyperoxic exposure to be associated with an increased risk for lung injury, although a lower risk than high tidal volumes and inspiratory pressures. In contrast, in actual clinical practice, the majority of PaO_2 values recorded in ICU patients are higher than recommended targets under comparable conditions and are generally accepted by ICU physicians and nurses without adjustment of ventilator settings.

Compared with previous studies from other countries, more respondents identified oxygen toxicity as a major threat to lung injury in ICU patients (59% compared with 26% and 51% in studies from Australia and Canada, respectively) (27, 28). Similar proportions of respondents considered high inspiratory oxygen concentrations a more important risk than high tidal volumes or inspiratory pressures, and a similar heterogeneity in self-reported attitudes regarding oxygen therapy was observed (27, 28, 39). The current results show generally higher minimum allowable SaO_2 ranges than data from Canadian intensivists (28), which may indicate that clinicians' beliefs have changed over the last decade or it may merely reflect geographical differences in oxygen therapy.

It appears that clinicians' opinions regarding optimal oxygen therapy are more variable in case SaO_2 is presented compared to PaO_2 as marker of oxygenation. For PaO_2, the vast majority of clinicians choose 7 to 10 kPa (52.5 to 75mmHg), whereas the preferred targets for saturation varied between 85% and 95%. Assuming that oxygenation targets should be in line with the best evidence in available guidelines, these preferred ranges may be triggered by recommendations and protocols providing comparable PaO_2 targets (30, 40). However, caution is urged when interpreting pulse oximetry to differentiate between hyperoxemia and normoxia. Saturation levels above 95% require special attention, since the corresponding PaO_2 levels usually cover a wide range and may substantially exceed target levels (24, 41).

According to the results from our questionnaire, the vast majority of respondents stated they would lower FiO_2 levels if PaO_2 was higher than 12 kPa (90 mmHg) or SaO_2 was higher than 95% in ARDS patients. The proportion of respondents that would lower FiO_2 is much lower if patients were presented with sepsis, cardiac and cerebral ischemia, or untreatable anemia. Unfortunately, we do not know whether respondents believe that oxygen is specifically harmful in patients with pre-existing acute lung injury or that higher oxygen levels are considered desirable in patients with ischemia or anemia. The latter hypothesis appears plausible, even though hyperoxemia has been reported to induce important vasoconstriction, which may lead to a paradoxical decrease in oxygen delivery (4, 42).

The self-reported low tolerance for higher PaO_2 or SaO_2 than target levels appears to be in contrast with actual treatment of patients in the same three ICUs where the survey was conducted. Neither FiO_2 nor PEEP was changed in the majority of cases when PaO_2 was higher than 15 kPa (112.5 mmHg) and FiO_2 was 40% or lower. In cases when FiO_2 was 40% to 100%, ventilator settings were adjusted more often, but even in these circumstances, hyperoxemia was accepted in approximately 20%. Considering the absence of definitive guidelines and robust controlled clinical evidence, this behavior in itself may still be justifiable (43). However, the contrast between self-reported attitudes

towards oxygen therapy on the one hand and actual treatment by the same healthcare workers on the other hand is striking.

The findings about oxygenation in ICU patients are consistent with previous findings from single center studies, showing that hyperoxemia was frequently present in mechanically ventilated patients and seldom led to adjustment of ventilator settings (31, 32). Clinicians may have specific reasons not to adjust ventilator settings when PaO_2 levels are higher than the target range. Indeed, we identified a considerable number of cases in which a presumed inadequate adjustment ultimately proved reasonable in the subsequent ABG sample (e.g., high PaO_2 followed by an increase in FiO_2, but resulting in a lower PaO_2). These cases may reflect scenarios in which clinicians anticipate deterioration in oxygenation or otherwise consider PaO_2 values as erroneous (e.g., arguably high PaO_2 – see Table 4, row PaO_2 > 30) or not representative for the current situation of a patient. Alternatively, it may be argued that hypoxemia harbors greater inherent hazards than hyperoxemia (3).

The differences between self-reported attitudes and actual treatment of patients should be interpreted with caution. First, the cases presented to the respondents included only limited details and do not reflect the complexity of clinical situations in daily practice. Further, we presented SaO_2 and PaO_2 categorized in ranges that were arbitrarily chosen. This may have influenced interpretation of the hypothetical cases. Second, ICU clinicians may have given more favorable responses in the online questionnaire due to social desirability and attention bias, although this is less likely as anonymous evaluation was secured. Third, the respondents were asked for the minimum allowable range in a specific ARDS case vignette, which may not reflect their beliefs regarding oxygen therapy in general. In the analysis of actually achieved oxygenation, we studied *all* patients independent of admission diagnosis. Also, response rates for the survey were relatively modest. However, the profession distribution in the group of respondents closely reflects a typical staff constitution in a general ICU in the Netherlands, which reduces the chance of sampling bias. In the Dutch clinical setting where respiratory therapists are not available, it is often the bedside nurse that responds first to changes in oxygenation. Therefore, the opinions of ICU nurses about oxygen therapy are important in the actual care of critically ill patients (39). Finally, some ABG samples, taken shortly after ICU arrival, may reflect oxygen therapy initiated on the operating room and influenced by anesthesiological ventilation strategies. However, successive ventilator adjustments were all recorded on the ICU and were supervised by critical care physicians. Therefore, high PaO_2 values in the direct postoperative period are not a plausible explanation for the low proportion of hyperoxic ABG samples not followed by adaptation of the ventilator settings.

Strengths of this study include the large sample of questionnaire responses and the extensive set of ABG data, derived from the same ICUs where the questionnaire was conducted. This facilitated a comprehensive comparison between self-reported attitudes and actual practices of oxygen therapy for both physicians and nurses. Further, the design of the present questionnaire closely resembles previous surveys from Canada and Australia, thereby exploring geographical patterns and trends in time concerning oxygen therapy. Our study extends these data as we have assessed objective data in our analysis including the successively measured PaO_2 after FiO_2 adjustment. This

allows further estimation of the effects of recorded FiO_2 adjustments in comparison with previous data (32).

CONCLUSIONS

This study shows that most clinicians acknowledge the potential adverse effects of prolonged exposure to hyperoxia, in accordance with emerging evidence for pulmonary toxicity and increased risk of poor outcome in both humans and animals caused by excessive oxygenation (2, 4, 6, 8, 16, 18, 20, 35, 44). However, objective data also suggest that clinicians did not consistently accommodate this conception in actual clinical practice and a large proportion of patients was exposed to arterial oxygen levels higher than self-reported as acceptable by nurses and physicians. Additional education, feedback, and implementation strategies, aimed at careful titration of oxygen, may therefore be an effective approach for strict adherence to oxygenation targets (45). Studies on the effects of different target ranges for PaO_2 on clinically relevant endpoints are needed to guide ICU professionals on how much oxygen should be administered to their patients.

LIST OF ABBREVIATIONS

ABG, arterial blood gas; FiO_2, fractions of inspired oxygen; ICU, intensive care unit; PaO_2, partial arterial oxygen pressure; PDMS, patient data management system; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation

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9

EFFECTIVENESS AND CLINICAL OUTCOMES OF A TWO-STEP IMPLEMENTATION OF CONSERVATIVE OXYGENATION TARGETS IN CRITICALLY ILL PATIENTS: A BEFORE AND AFTER TRIAL

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ABSTRACT

Objective

Conservative oxygen therapy is aimed at the prevention of harm by iatrogenic hyperoxia while preserving adequate tissue oxygenation. Our aim was to study the effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the ICU.

Design

This was a before and after stepwise implementation study of conservative oxygenation targets, between July 2011 and July 2014. The primary endpoint was the proportion of PaO_2 values within the target range. Secondary outcomes included ventilator-free days (VFDs) at day 28, length of stay (LOS), and mortality.

Setting

Three closed-format ICUs in the Netherlands.

Patients

We analysed data on 15,045 eligible admissions.

Interventions

The first implementation phase consisted of providing training and feedback on new guidelines instructing for explicit targets for arterial oxygen tension (PaO_2 55–86 mmHg) and oxyhemoglobin saturation (SpO_2 92–95%). In the second phase, bedside clinicians were additionally assisted in guideline adherence by a computerized decision-support system.

Measurements and Main Results

The proportion of PaO_2 in the target range increased from 47% at baseline to 63% in phase 1 and to 68% in phase 2 ($P<0.0001$). Episodes of hyperoxia decreased ($P<0.0001$), whereas hypoxic episodes remained unchanged ($P=0.06$) during the study. Mechanical ventilation time was significantly lower ($P<0.01$) during both study phases. After adjustment for potential confounders, VFDs in phase 1 and phase 2 were higher than baseline: adjusted mean difference 0.55 [95% CI 0.25, 0.84] and 0.48 [0.11, 0.86], respectively. Adjusted ICU mortality and intensive care unit free-days did not significantly differ between study phases. Hospital mortality decreased in reference to baseline: adjusted OR 0.84 [95% CI 0.74, 0.96] for phase 1 and 0.82 [95% CI 0.69, 0.96] for phase 2.

Conclusions

Stepwise implementation of conservative oxygenation targets was feasible, effective, and appeared safe in critically ill patients. The implementation was associated with several changes in clinical outcomes, but the causal impact of conservative oxygenation is still to be determined.

Trial registration: Netherlands Trial Register, number NTR3424

INTRODUCTION

The application of oxygen has always been of undisputed importance in emergency and critical care medicine. It is a highly effective therapy in preventing or compensating hypoxic injury and has life-saving properties. However, the risks of excessive oxygenation have recently placed the liberal use of oxygen in a new perspective. Oxygen is essential for cell metabolism and organ function, but triggers free radical formation and induces hemodynamic and inflammatory changes in higher doses (1-4). Furthermore, hyperoxia may promote lung injury during mechanical ventilation and has been linked to poor outcome in various subgroups (5-10). A considerable proportion of patients in the intensive care unit (ICU) is exposed to hyperoxia (11, 12), but preventive strategies may be hampered by a lack of clinical trials. Guidelines are available for a limited number of subgroups and are not easily extrapolated to universal recommendations for critically ill patients.

Conservative oxygen therapy is aimed at the prevention of iatrogenic hyperoxia while preserving adequate tissue oxygenation through careful oxygen titration (13, 14). This pragmatic strategy is increasingly advocated but its feasibility and effects on important clinical parameters are still to be assessed (15, 16). We hypothesized that a stricter adherence to conservative oxygenation guidelines may improve patient-centered outcomes by preventing derangements and inherent harm. Our aim was to study the effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the ICU.

MATERIALS AND METHODS

Study Design

This was a before and after stepwise implementation study of conservative oxygenation targets in the ICUs of three participating hospitals, including two academic and one large teaching hospital in the Netherlands. The participating ICUs are mixed medical and surgical, tertiary care units, with 20–30 beds, where full responsibility for the patient and treatment is transferred to the critical care physician.

The study was registered with the Netherlands Trial Register, number NTR3424. Ethical approval was granted by the Medical Ethical Committee of the Leiden University Medical Center. The need for informed consent was waived under Dutch National law for the type of study and in view of the retrospective and anonymous data collection.

Data Collection

Arterial blood gas (ABG) analyses, concurrent ventilator settings, and hourly pulse oximetry data recorded between July 1, 2011 and July 1, 2014 were extracted from the patient data management system (PDMS) databases (MetaVision, iMDsoft, Tel Aviv, Israel) of participating ICUs. Data were supplemented with anonymous demographic patient data, admission and discharge data, and data to quantify severity of illness from the Dutch National Intensive Care Evaluation (NICE) registry, a high quality database, which is subject to multiple quality checks and local audits in accordance with applicable research and ethical protocols (17).

All ABG data were used when analyzing the effects on oxygenation. For clinical endpoints, data were summarized per patient admission and in case of readmissions only the first admission was included. Analyses were conducted on data from all ICU patients with subgroup analyses on mechanically ventilated patients. Patients on extracorporeal membrane oxygenation were excluded from the study. Retrospective baseline analyses were performed over a 12-months period prior to the implementation and details have been described previously (11).

Procedures

At baseline, oxygen therapy was approached liberally and targets for the partial pressure of arterial oxygen (PaO_2) only specified a lower limit of 75 mmHg with liberal oxyhemoglobin saturation by pulse oximetry (SpO_2), in the participating hospitals. Local guidelines instructed for a fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP) depending on individual oxygenation measures and generally avoiding FiO_2 levels higher than 0.6 by increasing PEEP levels, instituting inverse-ratio ventilation, or prone positioning.

The first implementation phase of this study started at July 2012 and consisted of providing a written guideline, instructing to supply as little oxygen as possible with clear recommendations how to adapt oxygen administration and ventilator settings depending on ABG analyses. Guidelines were available as pocket cards, on posters, and electronically in participating hospitals. The study PaO_2 and SpO_2 targets were set between 55 and 86 mmHg, and 92–95%, respectively, and were chosen since they were considered safe, feasible, and consistent with previously suggested targets (18, 19). In patients with severe cardiac ischemia, cerebral ischemia, or untreatable anemia, higher target levels up to 105 mmHg were allowed. Repeated passive and interactive education on the rationale of conservative oxygenation targets and a clear description of preferred PEEP/FiO_2 combinations were provided to all ICU clinicians in the participating hospitals. Baseline strategies for protective ventilation remained unchanged and during all study phases guidelines instructed for tidal volumes between 6–8 ml/kg ideal body weight, PEEP levels between 5–24 cm H_2O, respiratory rate between 8–35 per minute and pH higher than 7.2. During the first study phase feedback was provided by statistical process control (SPC) and involvement of local leadership to promote a culture that supports guideline compliance. SPC was provided through newsletters and posters showing a summary of the guideline and the results of the previous time period including plots with mean and confidence interval statistics per week for oxygenation in range, PaO_2, SpO_2, FiO_2, and PEEP.

In the second and last phase of this study, from December 2013 till July 2014, a computerized decision-support system (CDSS) was introduced in the active, critiquing mode, meaning that it will automatically give decision-support, but only if the actual situation is not according to the guideline provided in phase 1 (20, 21). Raw data of all registered measurements were used for CDSS and filtered on data quality. A pop-up window appeared in the PDMS for bedside clinicians if either PaO_2 in ABG analysis was higher than the upper level or SpO_2 measurements were continuously higher than or equal to 97% for at least 30 minutes. The event was only triggered if the FiO_2 or PEEP level was not lowered within 40 minutes after registration of out-of-range oxygenation and

the previous notification was more than three hours ago. The notification window suggested to adjust oxygen administration and/or ventilator settings for a maximum of two times per shift and not within the first three hours of ICU admission. Measures from the first phase of implementation were also continued using repeated training and feedback. The implemented guidelines and CDSS were introduced with an intention-to-treat approach. Actual decisions to change the settings or targets were left to the discretion of the attending physicians and nurses in the ICU.

Outcomes

The primary endpoint was a priori defined as the proportion of PaO_2 values within the targeted study range. Secondary outcomes included ventilator-free days at day 28 after admission, duration of mechanical ventilation, length of stay (LOS), and mortality. PaO_2 according to study protocol was defined as 1) any PaO_2 in target range; 2) any PaO_2 higher than target range with concurrent FiO_2 at 0.21 and PEEP at 5 or followed by a decrease in FiO_2 or PEEP; 3) any PaO_2 lower than target range with concurrent FiO_2 at 1.0 and PEEP at 24 or followed by an increase in FiO_2 or PEEP. Hyperoxia was defined as any PaO_2 higher than 120 mmHg (22, 23) and hypoxia as any PaO_2 lower than 45 mmHg.

Mechanical ventilation time was calculated as the sum of all mechanically ventilated episodes during the same admission. The ventilator-free days (VFDs) were calculated as the number of ventilator-free days and alive, 28 days after ICU admission according to a previously described definition (24). Accordingly, the intensive care unit-free days (ICUFDs) were calculated as the number of days not spent in the ICU and alive at day 28. Oxygenation index was calculated as the FiO_2/PaO_2 ratio multiplied by the concurrent mean airway pressure. The standardized mortality ratio (SMR) was calculated using the APACHE IV predicted mortality.

Statistical Analysis

The study was designed to detect a 5% difference in the primary endpoint with 98% power, assuming 5000 ICU admissions in the participating hospitals per year.

Every set of ABG data and ventilator settings could be compared with the following set, as described previously (11, 25). Means with standard deviations and medians with interquartile ranges are provided according to the underlying distribution. In some cases, both means and medians are provided in order to comprehensively summarize the data. Differences between study phases were tested with ANOVA or Kruskal Wallis as appropriate. Multivariate analyses were performed using generalized linear regression models for ventilator-free and ICU-free days and logistic regression for mortality while adjusting for confounding covariates. Confounding variables were stepwise selected using the 10% change-in-estimate method (26). Propensity scores were included in the multivariate models in order to adjust for each patient's propensity to be admitted during either study phase. Variables included in the propensity score model were age, sex, hospital, APACHE III score, admission type, admission source, planned admission, co-morbidities, vaso-active drugs in the first 24 hours of admission and confirmed infection within 24 hours of admission. Mixed-effects models with random intercepts were performed to account for random effects within patients or hospitals. Inspection of the variance inflation factors indicated absence of important

multicollinearity in the multivariate models. All analyses were conducted using R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 0.98.1103 (RStudio Inc, Boston, MA).

RESULTS

In total, 295,701 ABG analyses were obtained over the baseline and implementation period. After excluding readmissions, 15,045 patients were included (Table 1). Eligible patients were predominantly male (64.2%), with a median age of 65 years. The majority of patients were mechanically ventilated at any time (81.8%) during admission and 17.3% was ventilated for more than 48 hours. Patient characteristics were comparable across study phases in terms of age, sex, body mass index, planned admission rate, illness severity, and several co-morbidities. The percentage of medical admissions increased from 33.7% at baseline to 36.8% in phase 1 and 38.1% in phase 2.

During the study, median levels of arterial oxygen pressures (PaO_2), oxyhemoglobin saturation (SpO_2) and central venous oxygen saturation ($ScvO_2$) decreased significantly (Table 1). Lactate was slightly higher during phase 2, but not during phase 1.

Arterial oxygenation

The proportion of ABG analyses with a PaO_2 in the targeted study range was markedly higher after implementation and increased from 47% during baseline to 63% in the first implementation phase and 68% during the second implementation phase (Table 2).

The mean difference between baseline and phase 1 was 16.1 [95% CI 15.8, 16.5] and 21.0 [95% CI 20.5, 21.5] between baseline and phase 2. The compliance showed a gradual increase during the 12 months of phase 1, but in comparison to the end of phase 1 no further improvement was found after implementation of the CDSS in phase 2 (Fig. 1).

The proportion of PaO_2 in range per patient admission, increased from 38% at baseline to 53% in phase 1 and 57% in phase 2. PaO_2 within target range as well as PaO_2 outside target range but promptly followed by adequate adjustments of oxygen administration or ventilator settings (PaO_2 according to study protocol) increased from 72% to 86% and 90%, respectively. The proportion of SpO_2 measurements in the target range increased from 16% to 25% and 27%, respectively. PaO_2 levels showed a rapid and persistent decline after the study start (supplemental figures, Supplemental Digital Content 1). The incidence of hyperoxia decreased from 15.3% during baseline to 9.0% and 7.6% in phase 1 and phase 2, respectively. The incidence of hypoxic episodes (<45 mmHg) did not essentially change (0.4% during baseline, 0.5% during both implementation phases).

In mechanically ventilated patients, the oxygenation index and FiO_2 levels decreased significantly during the study, along with an increase in PaO_2/FiO_2 ratio (Table 1). PEEP levels increased marginally in phase 2, and were adjusted less frequently than FiO_2 levels in all study phases. Mean airway pressures remained unchanged. Oxygenation higher than the upper study limit was less commonly observed after implementation and FiO_2 and PEEP levels were more frequently lowered in these cases (Table 2). Likewise, these ventilator settings were more frequently increased when PaO_2 levels were lower than the lower study limit.

Table 1. Descriptive characteristics

	All patients	Study phase			
		Baseline	Phase 1	Phase 2	P-value
Patient characteristics					
No. of patients	15,045	4,890	7,148	3,007	-
Demographics					
Age, years	65 (54-73)	65 (54-73)	65 (54-73)	65 (55-73)	0.60
Male, n	9665 (64.2%)	3171 (64.8%)	4595 (64.3%)	1899 (63.2%)	0.31
BMI, kg/m^2	25.8 (23.3-29.0)	25.7 (23.2-29.0)	25.8 (23.4-29.0)	26.0 (23.4-29.1)	0.22
Planned admission, n	7562 (50.3%)	2452 (50.1%)	3600 (50.4%)	1510 (50.2%)	0.97
Medical admission, n	5422 (36.0%)	1648 (33.7%)	2628 (36.8%)	1146 (38.1%)	<0.0001
Chronic health condition					
Acute renal failure, n	1105 (7.3%)	323 (6.6%)	547 (7.7%)	235 (7.8%)	0.05
Cancer, n	665 (4.4%)	206 (4.2%)	308 (4.3%)	151 (5.0%)	0.19
Cardiovascular disease, n	938 (6.2%)	308 (6.3%)	400 (5.6%)	230 (7.6%)	0.0005
Cirrhosis, n	277 (1.8%)	83 (1.7%)	118 (1.7%)	76 (2.5%)	0.01
COPD, n	1074 (7.1%)	313 (6.4%)	529 (7.4%)	232 (7.7%)	0.04
Diabetes, n	2609 (17.3%)	824 (16.9%)	1236 (17.3%)	549 (18.3%)	0.27
Renal disease, n	775 (5.2%)	231 (4.7%)	365 (5.1%)	179 (6.0%)	0.05
Respiratory disease, n	429 (2.9%)	160 (3.3%)	210 (2.9%)	59 (2.0%)	0.003
Severity of illness					
APACHE III score	53 (40-74)	53 (40-75)	54 (41-74)	53 (40-73)	0.42
APACHE IV predicted mortality, %	5.2 (1.4-22.5)	5.0 (1.3-22.9)	5.3 (1.5-22.2)	5.2 (1.5-22.3)	0.39
SAPS II score	34 (26-45)	34 (26-45)	34 (26-45)	34 (26-44)	0.29
SAPS II predicted mortality, %	15 (7-34)	15 (7-34)	15 (7-34)	15 (7-32)	0.28
Oxygenation and ventilation characteristics					
Arterial blood gas analyses, n	295,701	106258	137506	51937	-
PaO_2, mmHg	81 (70-98)	87 (74-107)	78 (68-93)	76 (67-89)	<0.0001
$PaCO_2$, mmHg	40 (35-46)	40 (35-46)	40 (35-47)	39 (34-45)	<0.0001
pH	7.42 (7.36-7.47)	7.41 (7.35-7.46)	7.42 (7.36-7.47)	7.43 (7.37-7.48)	<0.0001

Table 1. (continued)

		Study phase			
	All patients	**Baseline**	**Phase 1**	**Phase 2**	**P-value**
Hb, mmol/L	6.2 (1.2)	6.2 (1.2)	6.3 (1.2)	6.2 (1.3)	<0.0001
Lactate, mmol/L	1.5 (1.0-2.2)	1.5 (1.0-2.1)	1.4 (1.0-2.1)	1.6 (1.2-2.4)	<0.0001
Glucose, mmol/L[a]	7.6 (6.4-9.1)	7.5 (6.4-8.9)	7.6 (6.5-9.1)	7.8 (6.6-9.4)	<0.0001
Hourly pulse oximetry measurements, n	1,382,882	449,176	660,778	272,922	-
SpO_2, %	97 (95-99)	98 (96-100)	97 (94-99)	96 (94-98)	<0.0001
Venous blood gas analyses, n	17,753	4,817	8,811	4,125	-
$ScvO_2$, %	63.1 (10.4)	63.7 (10.7)	63.0 (10.4)	62.7 (10.2)	<0.0001
Ventilator settings					
FiO_2[c]	0.40 (0.31-0.50)	0.40 (0.40-0.50)	0.40 (0.30-0.45)	0.35 (0.30-0.45)	<0.0001
PEEP, cm H_2O[c]	7 (5-10)	7 (5-10)	7 (5-10)	8 (5-10)	<0.0001
Mean airway pressure, cm H_2O[b]	11 (9-14)	11 (9-14)	11 (9-14)	11 (9-14)	0.42
Oxygenation measures					
PaO_2/FiO_2 ratio	219 (165-291)	216 (164-285)	220 (165-291)	227 (168-300)	<0.0001
Oxygenation index[b]	3.8 (2.5-6.1)	3.9 (2.5-6.3)	3.8 (2.5-6.0)	3.7 (2.5-5.9)	<0.0001

Data are means (standard deviation), or medians (interquartile range) according to distribution, unless stated otherwise. Group comparisons between study phases were tested by ANOVA or Kruskal Wallis test according to distribution. Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation; SAPS, simplified acute physiology score; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; Hb, hemoglobin; SpO_2, oxyhemoglobin saturation; $ScvO_2$, central venous oxygen saturation; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure. [a] Glucose measurement from the ABG or closest to the time registration of the ABG was included, using a grace period of 10 minutes before or after ABG sampling. [b] Mean airway pressure and oxygenation index were assessed where requisite data was available (n=56,934). [c] FiO_2, PEEP is summarized data of ventilator settings at the time points of the concurrent ABG analyses measured during mechanical ventilation (n=186,513).

Table 2. Measures of implementation and oxygenation during all study phases

	Total	Study phase			
		Baseline	Phase 1	Phase 2	P-value
PaO_2 in target range, %	57.9	46.7	62.8	67.7	<0.0001
SpO_2 in target range, %	22.2	16.0	24.6	26.6	<0.0001
PaO_2 in target range per patient, %	48.6	38.0	52.5	56.8	<0.0001
PaO_2 according to study protocol, %	81.8	72.2	85.9	89.5	<0.0001
PaO_2 > upper study limit, %	39.4	51.3	34.1	29.0	<0.0001
of which followed by decrease in FiO_2 or PEEP, %[a]	*45.7*	*39.6*	*50.3*	*55.9*	*<0.0001*
PaO_2 < lower study limit, %	2.8	2.0	3.2	3.3	<0.0001
of which followed by increase in FiO_2 or PEEP, %[a]	*56.4*	*52.4*	*55.0*	*66.6*	*<0.0001*
PaO_2 > 120 mmHg, %	11.0	15.3	9.0	7.6	<0.0001
PaO_2 < 45 mmHg, %	0.4	0.4	0.5	0.5	0.06
ABG per patient, n	7 (4-16)	7 (4-17)	6 (4-16)	6 (4-15)	<0.0001
ABG per 24 hours, n	5 (4-6)	5 (4-7)	5 (4-6)	4 (3-6)	<0.0001

Abbreviations: ABG, arterial blood gas; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SpO_2, oxyhemoglobin saturation by pulse oximetry.
[a]Data in italics are subanalyses on mechanically ventilated patients of which PaO_2 was higher than the upper limit or lower than the lower limit.

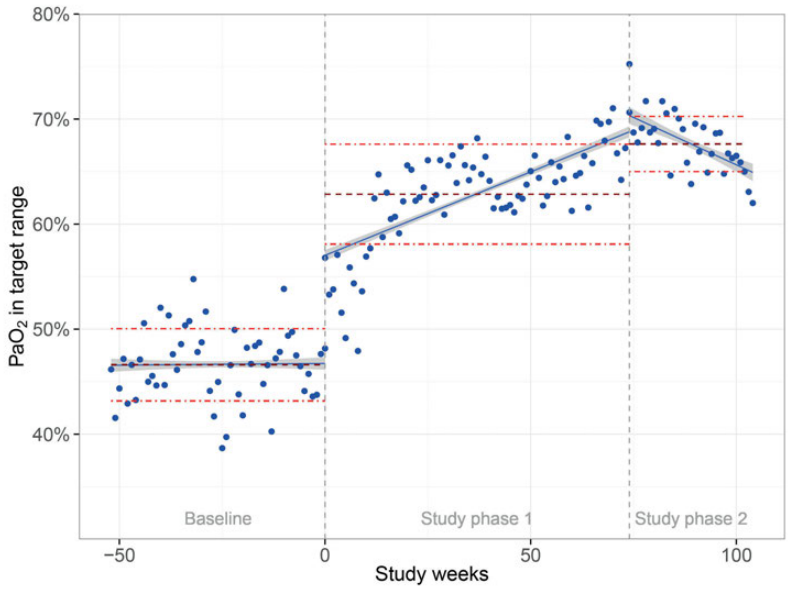

Figure 1. Percentage of arterial blood gas analyses in targeted oxygenation range during baseline and study phases.
Blue scatters are weekly means of primary outcome with weighted regression lines (95% CI) per study phase. Red horizontal lines are study phase means with SD

Table 3. Crude clinical outcomes during all study phases

		Study phase			
	Total	**Baseline**	**Phase 1**	**Phase 2**	**P-value**
All patients, n	15045	4890	7148	3007	-
ICU LOS					
Mean, days	3.4 (6.5)	3.4 (6.8)	3.5 (6.5)	3.4 (5.9)	0.72
Median, days	1.4 (0.8-3.1)	1.1 (0.8-3.0)	1.5 (0.8-3.2)	1.7 (0.9-3.6)	<0.0001
Hospital LOS					
Mean, days	14.3 (17.1)	14.7 (18.0)	14.2 (17.1)	13.8 (15.5)	0.04
Median, days	9 (6-16)	9 (6-16)	9 (6-16)	8 (5-16)	0.22
ICUFDs, days	21.6 (9.2)	21.5 (9.5)	21.7 (9.1)	21.6 (8.9)	0.63
ICU mortality, n	1487 (9.9%)	475 (9.7%)	709 (9.9%)	303 (10.1%)	0.86
Hospital mortality, n	2063 (13.7%)	723 (14.8%)	942 (13.2%)	398 (13.2%)	0.03
SMR [95% CI]	0.78 [0.75, 0.82]	0.84 [0.77, 0.90]	0.75 [0.70, 0.80]	0.76 [0.69, 0.84]	0.01
Mechanically ventilated at any time, n	12206 (81.1%)	4043 (82.7%)	5789 (81.0%)	2374 (78.9%)	0.0003
Mechanical ventilation time					
Mean, hours	46.9 (111.4)	50.7 (129.8)	46.0 (103.9)	42.5 (93.7)	0.01
Median, hours	10.8 (5.2-39.0)	11.4 (6.0-40.3)	10.8 (5.0-38.8)	9.4 (4.6-36.4)	<0.0001
ICU LOS					
Mean, days	3.8 (7.1)	3.8 (7.4)	3.9 (7.1)	3.8 (6.5)	0.63
Median, days	1.7 (0.9-3.8)	1.3 (0.8-3.6)	1.7 (0.9-3.8)	1.8 (0.9-4.0)	<0.0001
Hospital LOS, days					
Mean, days	14.3 (17.2)	14.7 (18)	14.3 (17.3)	13.7 (15.7)	0.09
Median, days	9 (6-16)	9 (6-16)	9 (6-16)	8 (6-15)	0.22
VFDs, days	22.3 (9.4)	22.1 (9.6)	22.5 (9.3)	22.5 (9.3)	0.10
ICUFDs, days	21.1 (9.6)	21.0 (9.8)	21.1 (9.5)	21.0 (9.4)	0.78
ICU mortality, n	1393 (11.4%)	452 (11.2%)	663 (11.5%)	278 (11.7%)	0.80
Hospital mortality, n	1802 (14.8%)	634 (15.7%)	824 (14.2%)	344 (14.5%)	0.13
SMR [95% CI]	0.80 [0.76, 0.84]	0.85 [0.78, 0.91]	0.77 [0.71, 0.82]	0.80 [0.71, 0.88]	0.01

Data are means (standard deviation), or medians (interquartile range) according to distribution, unless stated otherwise. Abbreviations: ICU, intensive care unit; LOS, length of stay; ICUFDs, intensive care unit-free days and alive at day 28; VFDs, ventilator-free days and alive at day 28; SMR, standardized mortality ratio according to APACHE IV model.

Secondary end points

Secondary outcome measures are listed in Table 3 and depicted in the supplemental figures.

ICU mortality and ICUFDs did not differ between study phases. The median ICU LOS was longer in phase 2 compared to phase 1 and baseline, whereas the mean ICU LOS remained unchanged. Median hospital LOS did not change and hospital mortality decreased from 14.8% during baseline to 13.2% during both implementation phases. Standardized mortality ratios and Kaplan-Meier curves for survival and mechanical ventilation time are shown in more detail in the supplemental figures.

For patients requiring mechanical ventilation at any time (n=12,206), median mechanical ventilation time decreased from 11.4 hours at baseline to 10.8 in phase 1 and 9.4 hours in phase 2.

Mortality rates showed no statistically significant change in this subgroup. The VFDs increased from 22.1 to 22.5 days after implementation. For the smaller cohort of patients who were ventilated for more than 48 hours (n=2,609), no significant differences for major outcome measures between study phases were observed (Supplemental Tables, Supplemental Digital Content 2). For surviving patients, mechanical ventilation time decreased, ICU LOS increased, whereas hospital LOS remained unchanged over the study time (Supplemental Tables, Supplemental Digital Content 2).

Separate analyses for the effect of the implementation in the individual participating ICUs are shown in the supplemental tables. Similar improvements in PaO_2 in target range were found in each ICU. In one of the units, the proportion of medical admissions increased markedly in phase 1 and phase 2, and potentially related to this, a concurrent increase in ICU LOS was found. The effect sizes of other outcome measures were in the same order of magnitude for all three ICUs.

Multivariate analyses

When the model for the proportion of PaO_2 samples in the target range was reanalysed in mixed-effects models, the associations were virtually unchanged (data not shown). The crude and adjusted estimates were calculated as mean differences or odds ratios per study phase in reference to baseline and were adjusted for identified confounders and propensity scores (Table 4). No increase in ICUFDs was found in either the unadjusted or adjusted analyses. After adjustment, the increase in VFDs was stronger. There were no statistically significant differences in ICU mortality, whereas the odds ratios for hospital mortality were lower in both implementation phases, after adjustment for confounders.

Table 4. Clinical outcomes with adjustment for confounders

	Study phase 1		Study phase 2	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Mean difference [95% CI]				
VFDs[a]	0.38 [0, 0.76]	0.55 [0.25, 0.84]*	0.39 [-0.08, 0.87]	0.48 [0.11, 0.86]*
ICUFDs[b]	0.16 [-0.17, 0.50]	0.16 [-0.11, 0.42]	0.08 [-0.34, 0.50]	0.10 [-0.23, 0.43]
Odds ratio [95% CI]				
ICU mortality[c]	1.02 [0.91, 1.16]	1.09 [0.93, 1.27]	1.04 [0.89, 1.21]	1.09 [0.90, 1.32]
Hospital mortality[c]	0.87 [0.79, 0.97]*	0.84 [0.74, 0.96]*	0.88 [0.77, 1.00]	0.82 [0.69, 0.96]*

Multivariate models were adjusted for admission type, APACHE III score and propensity score (for admission during either phase 1 or phase 2). Abbreviations: ICUFDs, intensive care unit-free days and alive at day 28; VFDs, ventilator-free days and alive at day 28. [a] Mean difference in ventilator-free days in reference to baseline for subgroup of mechanically ventilated patients. [b] Mean difference in intensive care unit-free days in reference to baseline for all patients. [c] Odds ratio (OR) for indicated mortality in reference to baseline for all patients. * P<0.05

DISCUSSION

Key findings

In this multicenter clinical trial, stepwise implementation of a strategy targeting conservative oxygenation levels through education, feedback, and decision support was shown to be feasible and effective in critically ill patients. Targeting PaO_2 levels of 55–86 mmHg and SpO_2 levels of 92–95% resulted in lower but safe oxygenation levels of arterial blood. Taking the before after design in consideration, this study was limited in the ability to address the clinical impact of our strategy. In adjusted analyses, implementation of the study protocol was associated with a slight improvement in ventilator-free days and hospital mortality. However, ICU-free days and ICU mortality were unaffected over the study time.

Interpretation

The proportion of PaO_2 samples in the target range (primary outcome) increased strongly in the first study phase in which traditional implementation strategies were applied. These strategies consisted of education for all ICU nurses and physicians, providing written guidelines on targets and ventilator settings, and frequent feedback using statistical process control. In contrast, the CDSS, which was offered in phase 2, had no additional effect on the primary outcome and may even have been somewhat counterproductive. However, phase 2 was shorter than phase 1 and trends could therefore be assessed with less precision. A ceiling effect of modifiable oxygenation should also be considered as ventilator settings are often initiated outside the ICU (e.g. during anesthesia or at the emergency room) and first ABG samples, taken shortly after ICU arrival, were responsible for an important part of these out-of-range samples. Other reasons for a ceiling effect can be postulated in terms of knowledge barriers, attitude barriers, and behavioral barriers (27). Barriers include reluctance of clinicians to adhere to new guidelines, resistance to change, and reluctance to replace pre-existing guidelines (28-30). Guideline implementation strategies were previously shown to be successful when strategies were multifaceted and actively engaged clinicians throughout the process (31). Although CDSS is usually beneficial (32), its effects in a multifaceted approach may be less (cost-)effective (33-35). An alternative explanation for the apparently paradoxical course of compliance in phase 2, is that traditional implementation was so successful that no additional benefit could be achieved by a decision support module. However, we cannot rule out that prolonged CDSS, different algorithms, more frequent reminders, or more specific suggestions to change ventilator settings, could have been more effective. During phase 2, the proportion of PaO_2 values within range was even somewhat lower than at the end of phase 1. Although this may be normal fluctuation by chance, decision support may alternatively induce passive behavior of bedside clinicians leading to slower adjustments of ventilator settings. Even after implementation of conservative oxygenation targets, approximately 30% of PaO_2 and 70% of SpO_2 measurements was higher than the target range. The latter marker of oxygenation is indeed less reliable and more variable, albeit the percentage of registered values increased significantly with implementation. The proportion of samples according to protocol, also including PaO_2 outside the limits followed by appropriate adjustments of oxygen and ventilator settings, was much better, reaching almost 90%

at the end of the study. In this respect, phase 2 was superior to phase 1, in line with other clinical outcome measures in multivariate analyses. Controlled evidence is warranted to further evaluate CDSS in comparison to traditional training and feedback (21).

Strengths and Limitations

The following potential limitations of this study should be considered. First, the non-randomized intervention in this clinical trial hampers causal inferences, especially regarding effects on relevant clinical patient outcomes. Differences in case-mix between the baseline period and both implementation phases may have been responsible for differences in outcomes such as length of stay, mechanical ventilation time, or hospital mortality. However, demographic characteristics and illness severity scores were very similar across the study periods and multivariate analyses were adjusted for confounders and propensity scores. The longitudinal design of this study yields potential bias as outcomes of ICU patients may improve over time due to factors other than oxygenation targets. Hypothesizing that attentive monitoring of oxygenation and ventilation improves outcome, study awareness may elicit attention bias. Indeed, we could not fully control for secular trends and potential changes in clinician behavior and ventilation management during the study. Interestingly, improvement of clinical outcomes was observed in all three ICUs during the first implementation phase, but without a further improvement after adding CDSS. Also, during the 12 months baseline period, no significant trends to improved survival, LOS, or mechanical ventilation time were found.

General oxygenation strategies were specified as much as possible, but specific and individual oxygenation strategies were left to the discretion of the participating centers and responsible clinicians. In this context, individual cases with amended target ranges including patients with severe anemia or ischemia were not specifically registered in the database. Hospital related differences in case-mix, patient care, and guideline adherence may accordingly influence the overall-effects, although there was a consistent signal for end points in the sensitivity analyses, even when wider PaO_2 target levels up to 105 mmHg were used for analysis. The only exception was ICU LOS which increased only in the ICU where an increase in the proportion of medical admissions was found. The finding that median ICU LOS increased during the study should therefore be interpreted with caution. Accordingly, in the multivariate analysis, also adjusting for admission type, no association between ICUFDs and implementation was found. Finally, our findings may not be directly generalizable to other ICUs although we believe that the inclusion of patients from three participating hospitals during two years can robustly represent a general ICU population. At least it shows the feasibility of conservative oxygen therapy with strict adherence to oxygenation targets.

Strengths of this study include the multicenter trial participation, the large patient cohort, the quality of the database, and the possibility to control for many covariates. Further, our findings are consistent with a previous single-center pilot study reporting compliance with targeted saturation in a small sample of mechanically ventilated patients (13). In this study, conservative oxygen therapy was shown to be free of adverse biochemical, physiological, and clinical outcomes. The present study confirms these findings on a larger scale and also demonstrates the feasibility of PaO_2 targets.

Clinical Implications

In mechanically ventilated patients, we could not demonstrate an improvement in mortality rates and LOS, yet mechanical ventilation time decreased in a significant manner. Potential mechanisms underlying the observed effects in clinical outcomes are multifarious. Precise control of arterial oxygenation avoids significant variation from the target range and may successfully reduce the harms associated with unnecessary extremes (15). In addition, conservative oxygen therapy may contribute to acclimatization and cellular adaptation to mild hypoxia, which may result in improved efficiency of ATP production and protection of mitochondria (15). Reducing the exposure to hyperoxia may decrease mechanical ventilation time by preventing absorption atelectasis, pulmonary inflammation, and other histopathological changes in the lung (1, 4, 9). Patient-centered outcomes are also likely to be impacted by reactive oxygen species, oxygen-induced cardiovascular alterations (2), oxidative DNA damage (36) and mediators of oxygenation. Interestingly, hospital mortality decreased during the study whereas ICU mortality remained unchanged. This observation is in agreement with results from pooled cohort studies, showing that arterial hyperoxia was associated with hospital mortality but not specifically with ICU mortality (10). Clinical improvements may alternatively be attributed to behavioral changes in clinical practice and precise control of oxygenation, rather than to the prevention of hyperoxia per se (37).

The oxygenation ranges used in this study were chosen based on previous recommendations (18, 19). In accordance, this range was within the standard of care and no reasonably foreseeable risks of the actually achieved oxygenation were anticipated. Although other target ranges for conservative oxygen therapy may well be as good as or even better than the range we studied (14), our approach was safe in terms of major clinical end points. Also, the incidence of severe hypoxia was rare and did not increase over time. In comparison to baseline, tissue oxygenation represented by arterial lactate or oxygenation index did neither deteriorate. Moreover, the higher percentiles of lactate levels remained virtually unchanged (data not shown). In prospective evaluation of conservative oxygenation, a randomized intervention, alternative mediators and the effects on specific parameters including hemodynamics and the microcirculation are still to be assessed.

CONCLUSIONS

Stepwise implementation of conservative oxygenation was feasible and showed a rapidly established high compliance to targeted arterial oxygen and saturation levels. The gradual improvement in guideline adherence was accompanied by a slight improvement in several clinical outcomes, but this should be interpreted with caution in view of the study design. Future randomized controlled studies should further clarify the causal effects of oxygenation targets on clinical outcomes for ICU patients.

DECLARATION OF INTERESTS

We declare no competing interests regarding this work. Dr. Bosman reports personal fees from consultant work for IteMedical, Dutch supplier of the PDMS, outside the submitted work. The funders

of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

ONLINE SUPPLEMENT

For the online supplements, please use the following weblinks, or scan the QR-codes with your mobile device

Supplemental Figures. Supplemental Digital Content 1: http://links.lww.com/CCM/B530

Supplemental Tables. Supplemental Digital Content 2: http://links.lww.com/CCM/B531

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9a

TO THE EDITOR: OXYGEN AS AN ESSENTIAL MEDICINE: UNDER- AND OVER-TREATMENT OF HYPOXEMIA IN LOW- AND HIGH-INCOME NATIONS

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In a recent issue of Critical Care Medicine, Helmerhorst et al. (1) made two important points. First, hyperoxia is associated with significant morbidity and mortality. Second, an intervention with minimal cost, involving training and provider feedback, decreased improper use of oxygen by 25% ($p < 0.0001$), ensuring that 63% of patients received appropriate therapy (SpO_2 , 92–95%). This modest intervention resulted in a significant decrease in hospital mortality and mechanical ventilation time. However, in low-income nations, undertreatment of hypoxemia, as opposed to the "more is better" scenario addressed by Helmerhorst et al. (1), is still a problem. A single study found that the point prevalence of undiagnosed hypoxemia was 9% among 109 inpatient adults in Zambia (2). In 2015, the Lancet Commission on Global Surgery found that 24% of developing country hospitals lack oxygen, and 70% of operating theaters do not have pulse oximeters (3). Our group sought to determine the occurrence rate of hypoxemia and associated mortality among all inpatient adults in a low-income setting. We conducted a prospective single-center observational study in one of Rwanda's two public tertiary care hospitals, with 12,000 annual admissions (4). We screened all adult inpatients (age > 15yr) every day for 4 weeks in 2014 with an Acare/Lifebox oximeter (Acare Technology Co., Ltd., Taipei, Taiwan). Hypoxemia was defined as oxygen saturation less than 90% or receiving oxygen supplementation. During the 4 weeks of the study, 1,046 adult patients were admitted to the hospital (4). One hundred twenty-six patients (12.0%) were hypoxemic on one or more days with an inpatient mortality rate of 49.2%. Median age was 49 years (interquartile range (IQR), 34–65 yr). Mortality was worse with worsening hypoxemia. As hypoxemia increased from mild, moderate, to severe, corresponding mortality rates increased from 30.8% to 40.7% to 57.4% (estimated PaO_2-to-Fio_2 ratio between 200 and 300; 100–200; < 100), respectively. While 111 patients (88.1%) received adequate oxygen at least 1 day, 76 (60.3%) of hypoxemic patients either received no oxygen therapy or inadequate oxygen therapy on at least 1 day (SpO_2 < 90%). Median time from admission to hypoxemia was 1 day (IQR, 1–3 d). Oxygen has been listed as one of the World Health Organization's Essential Medicines since the first online edition was published in 2002 (5); however, very little research exists on hypoxemia in adult populations. In our study of inpatient adults, hypoxemia occurred at epidemic proportions. Although 85.7% of hypoxemic patients were in hospital wards outside the ICU, their 49.2% mortality rate was almost identical to the mortality of our ICU patients (47.1%) (4). It is possible that hypoxemia is simply a marker of severe disease; however, our data raise the question of whether consistent oxygen therapy at all levels of the health system could make an impact on mortality. While Helmerhorst et al. (1) study rightly emphasizes that more oxygen is not always better, "some" oxygen to address hypoxemia is almost certainly beneficial. Helmerhorst et al. (1) trial indicates that simple, low cost educational and behavioral interventions are capable of improving oxygen use where oxygen is available and hyperoxia a common occurrence. For much of the world, making oxygen consistently available and educating on the need to avoid hypoxemia remain the priority.

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9b

THE AUTHORS REPLY

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We thank Sutherland et al. (1) for their interest and thoughtful comments regarding our work. They have raised an important issue that regional differences play a key role in oxygen management and that insufficient availability may contribute to higher mortality rates as shown by Riviello et al. (2). Despite the potential risks of excessive oxygenation, it is extremely important to realize that oxygen has life-saving properties in many critical conditions. This accounts for all patients worldwide, but Sutherland et al. (1) duly emphasize that its availability is not self-evident in all countries. Especially in low-income nations, meeting the basic needs of oxygen should receive first priority as long as hypoxemia imposes a major threat to public health. Indeed, sufficient oxygen therapy is vital for all levels of the health system, and adequate training and education on the accessibility, use, and misuse of oxygen remain crucial. This makes it even more pertinent that our study showed that clinicians' behavior regarding oxygen management can be (permanently) changed by simple and universal measures such as education, feedback, and training (3). We also showed that, with increased focus on conservative oxygen therapy, hypoxemic events were more adequately acted upon during our study period. Computerized decision support may be of added value in this context but should be further studied and may not be universally available in all health institutions.

A second issue that Sutherland et al. (1) address is adequate recognition and treatment of hypoxemia. Early diagnosis by pulse-oximeters and point-of-care blood gas analyzers are prerequisites for optimal oxygen therapy, avoiding both hypoxemia and hyperoxia. Furthermore, tailored oxygen administration through nasal cannulas, masks, or ventilators and appropriate titration of the dose determine the success of the intervention. These assets are essential for patient-centered outcome and are impacted by the (financial) resources and focus of the institution and caregivers.

We believe that our study yielded hopeful results for further implementation of targeted oxygen management, and we intend to persevere on studying on the safety and effectiveness of such measures.

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10

GENERAL DISCUSSION AND SUMMARY

PLEADINGS

This thesis addresses the clinical challenge of providing the right amount of oxygen to critically ill patients.

In the first part we reviewed the literature for the experimental and clinical effects of inspired and arterial hyperoxia (**chapter 2**). Sufficient oxygen supply is essential for human survival and administering high levels of inspired oxygen is therefore a powerful and efficient tool to prevent the life-threatening effects of hypoxia in critically ill patients. However, excessive oxygenation also has deleterious properties in various pathophysiological processes. The effects of supplemental oxygen prove to be diverse and reactive oxygen species play an important role in hyperoxia-mediated tissue injury and oxidative stress, characterized by cell damage, cell death and inflammation. When human lungs are continuously exposed to hyperoxia, symptoms start locally with tracheobronchitis, atelectasis, pulmonary edema, and eventually respiratory failure. Symptoms may also spread to the central nervous system, as evidenced by nausea, dizziness, headache, visual disturbances, neuropathies and convulsions. Vascular effects originate rapidly and include vasoconstriction in most vascular beds. The increase in systemic vascular resistance may prove useful in counteracting unfavourable vasodilation during shock or anesthesia, but may also impair cardiac output and organ perfusion. We concluded that oxygen remains of life-saving importance in critical care, but can also be toxic in higher doses and after prolonged exposure. We must further stress that evidence from experimental models that are clinically relevant to the critical care setting were scarce and the effects of hyperoxic exposure on critically ill patients requires further research due to the lack of robust evidence from clinical studies.

As a proof of principle, we further investigated which effects prolonged hyperoxia has in a preclinical context (**chapter 3**). By exposing mice to increasing levels of inspired oxygen during mechanical ventilation, we found that hyperoxia has a time- and dose dependent effect. We demonstrated a severe vascular leakage and a pro-inflammatory pulmonary response in mechanically ventilated mice, which was enhanced by hyperoxia and longer duration of mechanical ventilation. Prolonged ventilation with high oxygen concentrations induced a time-dependent immune response characterized by elevated levels of neutrophils, cytokines and chemokines in the pulmonary compartment, which was not directly translated into extensive lung injury. This was in line with previous findings even though remarkable differences in cytokine levels were noted and lung injury scores were comparable between the study groups. The complex kinetics and dynamics of the immune response make it very difficult to characterize the exact mechanisms, interpret the effects and attribute these to a specific part of the combined exposure to anesthesia, mechanical ventilation and hyperoxia. Moreover, translation of these study results to the clinical situation remains cumbersome as healthy mice are not identical to critically ill patients. Our experimental model may be a useful representation of the intensive care setting and may aid to determine optimal ventilator strategies in critically ill patients but needs further modification and validation to test new hypotheses, acquire more insight in save oxygen management and generate further leads for clinical implementation.

In the second part of this thesis, we focused on the clinical effects of hyperoxia and the associated outcomes in critical illness. Concentrating on the vascular effects of clinical implementation, we experimentally introduced a brief hyperoxic interval in the postoperative period of mechanically ventilated patients in the ICU after coronary artery bypass grafting surgery (**chapter 4**). We evaluated the acute hemodynamic changes and aimed to comprehensively describe alterations of the circulation by measuring cardiac output, mean systemic filling pressure, resistance to venous return, cerebral blood flow velocity and markers of the microcirculation. During a 15-minute exposure to hyperoxia, we observed significant alterations in systemic circulation mainly by vasoconstriction of both the venous and arterial circulation and an increase of mean systemic filling pressure. Effects on cardiac output, cerebral blood flow and the microcirculation were relatively small and may be clinically insignificant in hemodynamically stable subjects. However, the increase in systemic resistance, stressed volume and systemic filling pressure by hyperoxia resembled the effects of norepinephrine and associated changes in central circulatory variables may have clinically important consequences in critically ill patients when hemodynamic changes are vital. These findings underscore the potential benefit of inducing hyperoxia during vasodilatory shock, but may also explain why patients with acute cardiac ischemia have a greater myocardial infarct size after supplemental oxygen therapy in the ambulance and during cardiac catheterization. Furthermore, these results shine light on associations found between arterial hyperoxia and in-hospital mortality among patients admitted to the ICU following resuscitation from cardiac arrest.

In order to further appraise this relationship, we examined the separate and combined effects of the partial pressures of both arterial carbon dioxide and arterial oxygen in a multicenter cohort of patients admitted to Dutch intensive care units after cardiac arrest (**chapter 5**). We exhibited the survival probability inferred from continuous levels of $PaCO_2$ and PaO_2, revealed a U-shaped relationship with mortality for both parameters, and found that hypocapnia and hypoxia were independently associated with hospital mortality in post cardiac arrest patients. A synergistic effect of concurrent derangements of $PaCO_2$ and PaO_2 was not observed, but the close relationship between both parameters argues for a concurrent assessment of the effects and we concluded that accurate evaluation of target ranges is warranted.

With regards to arterial oxygenation, we systematically reviewed the literature for cohort studies comparing hyperoxia to normoxia in critically ill adults and performed a meta-analysis and meta-regression of the results (**chapter 6**). Nineteen studies were pooled and showed that arterial hyperoxia during admission decreases hospital survival. Functional outcome measures were diverse and generally showed a more favorable outcome for normoxia. Considering the substantial heterogeneity of included studies and the lack of a clinical definition, we interpreted that more evidence was needed to provide optimal oxygen targets to critical care physicians.

We challenged this conclusion by evaluating previously used and newly constructed definitions of arterial hyperoxia (metrics) and systematically assess their association with clinical outcomes in different subgroups in the intensive care unit (**chapter 7**). Severe hyperoxia was associated with higher mortality rates and fewer days on the mechanical ventilator in comparison to both mild hyperoxia and normoxia for most metrics. Adjusted effect estimates for hospital mortality were larger for severe hyperoxia than for mild hyperoxia. This association was found both within and

beyond the first 24 hours of ICU admission and was consistent for large subgroups. The largest point estimates were found for the exposure identified by measures of central tendency (average and median PaO_2) and these estimates differed substantially between subsets. Time spent in hyperoxia showed a linear and positive relationship with hospital mortality. This led us to conclude that we should limit the PaO_2 levels of critically ill patients within a safe range, as we do with other physiological variables.

In the third part of this thesis, we studied current oxygen management and explored strategies to support guideline adherence regarding oxygen therapy. In order to pursue this, we identified common beliefs and self-reported attitudes of critical care physicians and nurses on oxygenation targets and compared this with actual treatment of patients in three tertiary care intensive care units in the Netherlands (**chapter 8**). Most ICU clinicians acknowledge the potential adverse effects of prolonged exposure to hyperoxia and report a low tolerance for high oxygen levels. However, in actual clinical practice, a large proportion of their patients was exposed to higher arterial oxygen levels than self-reported target ranges.

Following these results, we subsequently studied the feasibility, effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in the same three intensive care units (**chapter 9**). With education, feedback and a computerized decision support system, we recognized that stepwise implementation of conservative oxygenation targets was feasible and showed a rapidly established high compliance to targeted arterial oxygen and saturation levels. Targeting PaO_2 levels of 55-86 mmHg and SpO_2 levels of 92–95% resulted in lower but safe oxygenation levels of arterial blood. The gradual improvement in guideline adherence was accompanied by a decrease in mechanical ventilation time and hospital mortality, but this should be interpreted with caution in view of the before-after design of this study. Future randomized controlled studies should further clarify the causal effects of oxygenation targets on clinical outcomes for ICU patients.

WITNESS AND JURY

The side-effects of hyperoxia can be roughly subdivided in cell damage, inflammation, pulmonary complications, neurological symptoms and vascular effects. These major features are responsible for the large majority of the unfavourable effects and increased risk for morbidity and mortality following (prolonged) exposure to hyperoxia.

As a result of oxygen free radicals (reactive oxygen species) and damage associated molecular patterns (DAMPs), DNA and cell damage may manifest as apoptosis and necrosis leading to tissue injury and local organ-specific complications. DNA damage has been suggested to underlie the worse outcomes of cancer patients exposed to high FiO_2 levels during oncological surgery (1, 2). Pathways of cell damage and oxidative stress contribute to a pro-inflammatory state in which tissue injury is exaggerated and the innate immune system may be impaired. Neurological symptoms can be transient or severe but are usually less pertinent and difficult to diagnose in sedated critically ill patients. Pulmonary complications, however, are more frequently encountered as atelectasis and pulmonary edema can have major influence on oxygenation and ventilation parameters. Furthermore, vascular effects, including vasoconstriction and bradycardia, may result in impaired

organ perfusion. Likewise, increased mortality and morbidity have been observed with hyperoxia during events such as ischemic heart disease (3), cardiac arrest (4, 5), stroke (6, 7), traumatic brain injury and mechanical ventilation.

Interestingly, it has long been suggested that hyperoxia may have anti-bacterial properties and can reduce surgical site infections or infectious complications, but in recent meta-analyses this effect appeared to be marginal or even absent (8, 9). Pursuing prolonged periods of supraphysiological oxygenation may thus not have any beneficial effect compared to normoxia. As the risk of adverse events may be increased by a FiO_2 of 60% or higher, and as robust evidence is lacking for a beneficial effect, evidence is still insufficient to support the routine use of hyperoxia during anesthesia, surgery and mechanical ventilation of non-injured lungs (10).

In the ICU setting, clinical practice guidelines generally target oxygen levels in arterial blood comparable with healthy adults at sea level (11-13). Recently published trials comparing conservative with conventional or maximal oxygen therapy (14, 15) show potential benefits for conservative oxygenation which is in keeping with the results of the Oxytar trial (16), but contrasts with results of a pilot randomized controlled trial (RCT) that demonstrated the feasibility and safety of conservative oxygen administration (17).

RULING AND VERDICT

From this thesis, we conclude that careful oxygen titration and monitoring is the best therapeutic strategy aimed at the prevention of potentially dangerous hyperoxia while preserving adequate tissue oxygenation. In this context, conservative oxygenation in the intensive care unit is a promising strategy to achieve better clinical outcomes for critically ill patients. Importantly, the beneficial effects of sufficient oxygen supply should not be undervalued in attempts to prevent hyperoxia and pursue conservative oxygenation. In critical situations, administering oxygen remains essential to prolong the window of opportunity and provide as much oxygen as necessary in anticipation of (e.g. pre-oxygenation), or during arterial hypoxia (e.g. respiratory failure, carbon monoxide intoxication, gas embolism, decompression sickness), and to rapidly establish pulmonary vasodilation (e.g. in right-sided heart failure) or systemic vasoconstriction (e.g. in vasodilatory shock), when other measures are inadequate or fail. At the same time, clinicians should be well aware of the side-effects that are induced by supplying high levels of oxygen, as hyperoxia is also frequently encountered in critically ill patients.

Given the risk of bias in the available evidence, definitive recommendations in providing the right dose of supplemental oxygen are not yet obtainable and further RCTs from robust methodological quality are warranted. Some RCTs have provided further leads for patients in specific subsets and several more trials have recently been initiated. In selected patients, targeting the lower ranges of normoxia (55-80 mmHg) can be safely pursued. In expectation of compelling evidence from future clinical trials, targeting relative normoxia (80-150 mmHg) by avoiding exposure to both subphysiological as well as supraphysiological oxygenation should be considered the most rational choice in most cases.

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NEDERLANDSE SAMENVATTING
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NEDERLANDSE SAMENVATTING

Bij een aanzienlijk deel van patiënten op de intensive care (IC) afdeling wordt het ademen ondersteund met een beademingsmachine. Zuurstoftoediening kan hierbij van levensreddend belang zijn om het lichaam van voldoende zuurstofrijk bloed te voorzien tijdens een kritieke ziekteperiode. Ondanks het grote belang van deze behandeling zijn er aanwijzingen dat beademing met hoge zuurstofconcentraties de kans op complicaties en zelfs overlijden op de IC vergroot. Er wordt dus vermoed dat overdaad schaadt. De mechanismes die leiden tot complicaties zijn echter nog onvoldoende opgehelderd maar zijn van essentieel belang in de behandeling en preventie van zuurstofschade bij beademde patiënten.

Dit proefschrift gaat in op de klinische uitdaging voor zorgverleners om de juiste hoeveelheid zuurstof toe te dienen aan kritisch zieke patiënten. In het eerste deel van dit proefschrift wordt de huidige stand van zaken beschreven op het gebied van de fysiologische, (dier)experimentele en klinische effecten van hoge concentraties zuurstof (*hyperoxie*) in de ingeademde lucht en in het slagaderlijke bloed.

In **hoofdstuk 2** beschrijven we dat voldoende zuurstofvoorziening essentieel is voor het menselijk bestaan en dat de toediening van een hoge dosis zuurstof een krachtig en efficiënt middel is om een levensbedreigend zuurstoftekort bij kritisch zieke patiënten te voorkomen. Teveel zuurstof heeft echter ook nadelige gevolgen in een aantal ziekteprocessen. De effecten van zuurstoftoediening zijn divers en zuurstofradicalen spelen een belangrijke rol bij de weefselschade door celschade, celdood en ontstekingsreacties (de zogenaamde 'oxidatieve stress'). Op het moment dat onze longen continu blootgesteld worden aan hyperoxie, beginnen de symptomen van zuurstofvergiftiging vaak met een lokale ontstekingsreactie, het samenvallen van longblaasjes (atelectase), een toename van longvocht (longoedeem), en op den duur kan de ademhaling zelfs volledig falen. De symptomen kunnen zich verspreiden naar het centrale zenuwstelsel, waarbij er misselijkheid, duizeligheid, hoofdpijn, visusklachten, gevoelsstoornissen en convulsies kunnen ontstaan. De effecten op de bloedvaten kunnen zich heel snel manifesteren, waarbij de bloedvaten vrijwel overal in het lichaam, met uitzondering van de longen, samenknijpen (vasoconstrictie). Hierdoor ontstaat een toename in de systemische vaatweerstand en bloeddruk. Dit kan gunstig zijn in het geval van een lage bloeddruk met vaatverwijding (vasodilatatie) bij shock of na het geven van narcosemiddelen (anesthetica), maar kan ook het hartminuutvolume en de weefseldoorbloeding verminderen. Op basis van deze bevindingen concluderen we dat zuurstof van levensreddend belang blijft in spoedeisende situaties en op de IC, maar dat zuurstof ook toxisch kan zijn in hogere doses en na langdurige blootstelling. Bovendien moeten we benadrukken dat het bewijs voor zuurstoftoxiciteit uit experimentele studies, die klinisch relevant zijn voor de IC setting, mager en onvoldoende is. Doordat er gelijktijdig een gebrek is aan goed uitgevoerde, klinische studies, behoeft het effect van hyperoxie bij kritisch zieke patiënten zonder twijfel meer onderzoek.

Om meer inzicht te krijgen in de effecten van langdurige hyperoxie in een preklinische context hebben wij in **hoofdstuk 3** gebruik gemaakt van een experimenteel beademingsmodel. Door muizen bloot te stellen aan oplopende hoeveelheden zuurstof met een beademingsmachine, hebben we laten zien dat hyperoxie een tijds- en dosis-afhankelijk effect heeft. We hebben aangetoond

dat door de beademing de longvaten kunnen gaan lekken en dat er een ontstekingsreactie in de longen van muizen ontstaat. De beademingsduur en de mate van hyperoxie zijn hierbij belangrijke determinanten voor de longschade en -ontsteking. Langdurige beademing met hoge concentraties zuurstof veroorzaakte een tijdsafhankelijke reactie die gepaard gaat met verhoogde waardes van witte bloedcellen en andere ontstekingsmediatoren in longvocht. Dit komt overeen met resultaten uit voorgaande studies maar er zijn ook opvallende verschillen in de concentratie van de ontstekingswaarden. Bovendien zijn de scores voor longschade vergelijkbaar in de verschillende zuurstof-studiegroepen. Dit kan verklaard worden door de complexiteit van de immuunreactie waarbij het ingewikkeld is om de verschillende waarden specifiek toe te schrijven aan de verschillende onderdelen van de gelijktijdige blootstelling aan narcose, mechanische beademing en hyperoxie. Daarnaast blijft het complex om de experimentele resultaten eenduidig naar de klinische praktijk te vertalen. Ondanks dat gezonde muizen niet identiek zijn aan kritisch zieke mensen, kan ons experiment een bruikbaar model zijn voor de intensive care setting. Het kan bijdragen aan de zoektocht naar optimale beademingsstrategieën, maar het model behoeft validatie en verdere aanpassingen om nieuwe hypotheses te testen, meer inzicht te geven in veilige omgang met zuurstof en nieuwe aanknopingspunten te genereren voor de klinische toepasbaarheid.

In het tweede gedeelte van dit proefschrift ligt de focus op de klinische gevolgen van hyperoxie en de gerelateerde uitkomsten in kritieke fases van ziekte. In **hoofdstuk 4** hebben we ons geconcentreerd op de effecten van hyperoxie op de bloedvaten. Daartoe hebben we beademde patiënten een korte periode blootgesteld aan hoge fracties zuurstof in de inademingslucht, terwijl zij op de intensive care waren opgenomen nadat ze een bypass van de kransslagaders van het hart hadden ondergaan. Tijdens deze periode hebben we de veranderingen in de hemodynamiek (circulatie en drukken van het hart- en vaatsysteem) van de patiënten geëvalueerd. Daarbij zijn ook de veranderingen in de hersendoorbloeding en doorbloeding van de kleine haarvaten (microcirculatie) in acht genomen. Tijdens een 15-minuten-durende blootstelling aan hyperoxie hebben we waargenomen dat er significante veranderingen optraden in de bloedcirculatie. Deze veranderingen worden voornamelijk veroorzaakt door het samenknijpen van de bloedvaten in zowel het slagaderlijke (arteriële) als aderlijke (veneuze) systeem. We hebben hierbij opgemerkt dat de bloeddruk stijgt ten gevolge van de blootstelling aan hoge fracties zuurstof. Ook de druk die overblijft tijdens een hypothetische stilstand van de bloedsomloop (bijvoorbeeld tijdens een hartstilstand) kon worden nagebootst in een model en liet een belangrijke toename zien tijdens hyperoxie. De effecten op de output van het hart, de hersendoorbloeding en de microcirculatie zijn relatief klein en kunnen van ondergeschikt belang zijn in stabiele gezonde patiënten. De toename in de vaatweerstand door hyperoxie blijkt daarentegen goed overeen te komen met eerder aangetoonde effecten van het vaak toegediende hormoon noradrenaline als medicament. De daarmee gepaard gaande veranderingen in de hemodynamiek kunnen klinisch van groot belang zijn bij kritisch zieke IC patiënten. Deze bevindingen benadrukken het potentiële nut dat hyperoxie kan hebben als een patiënt zich in een kritieke fase van shock bevindt met een bijkomende lage bloeddruk. Het laat echter ook zien hoe patiënten met een acute vernauwing of verstopping van de kransslagaders een groter hartinfarct kunnen krijgen als er zuurstof toegediend is in

de ambulance of tijdens de hartkatheterisatie. De resultaten kunnen ook een recent aangetoond verband verklaren tussen hyperoxie en ziekenhuissterfte bij patiënten die na een hartstilstand en reanimatie op de intensive care worden opgenomen.

Om dit verband nader in kaart te brengen onderzochten we de onafhankelijke en gecombineerde effecten die de waarden van zuurstof (PaO_2) en koolstofdioxide ($PaCO_2$) in het slagaderlijke bloed hebben in patiënten die na een hartstilstand opgenomen zijn geweest op Nederlandse intensive care units (**hoofdstuk 5**). Daarbij hebben we laten zien dat zowel lage als hoge opnamewaarden van $PaCO_2$ en PaO_2 de overlevingskans negatief beïnvloeden (U-vormige curve). Hypocapnie (verlaagd $PaCO_2$) en hypoxie (verlaagd PaO_2) zijn voor deze patiënten onafhankelijke voorspellers van toegenomen sterfte. We zien hierbij geen versterkt (synergistisch) effect van gelijktijdige afwijkingen in zowel $PaCO_2$ als PaO_2, maar de nauwe verwantschap tussen zuurstof en koolstofdioxide rechtvaardigt een gelijktijdige beoordeling van de effecten. We concluderen dat nauwkeurige evaluatie van deze streefwaarden derhalve essentieel is.

Ten aanzien van de slagaderlijke zuurstofwaarden, hebben we in de literatuur gezocht naar cohortstudies die hyperoxie vergelijken met normoxie (zuurstof binnen de normaalwaarden) bij kritisch zieke patiënten. Deze studies hebben we systematisch beoordeeld en opgenomen in een meta-analyse (**hoofdstuk 6**). We hebben negentien studies gevonden die aan de inclusiecriteria voldeden. Door de resultaten van deze studies te combineren hebben we aangetoond dat hyperoxie in het slagaderlijke bloed gedurende de IC-opname sterk geassocieerd is met een verhoogde kans op ziekenhuissterfte. Voor functionele uitkomstmaten zijn de resultaten van de verschillende studies divers, maar over het algemeen laten dezen een gunstigere uitkomst zien voor patiënten met zuurstof binnen de normaalwaarden. De geïncludeerde studies zijn sterk uiteenlopend en met het oog op het gebrek aan een duidelijke klinische definitie van hyperoxie hebben we geconstateerd dat er meer bewijs nodig is om optimale zuurstofstreefwaarden vast te stellen.

Deze conclusie hebben we vervolgens getest door de klinische uitkomsten, gebaseerd op nieuwe en bestaande definities van hyperoxie, in verschillende IC patiëntengroepen te onderzoeken (**hoofdstuk 7**). Ernstige hyperoxie blijkt geassocieerd met een hoger sterfterisico en minder beademingsvrije dagen op de IC in vergelijking met zowel milde hyperoxie als normoxie (licht verhoogde of normale zuurstofwaarden). Deze associatie gaat op voor de meest gebruikte definities van hyperoxie bij verschillende grote subgroepen en blijft bovendien bestaan als we corrigeren voor mogelijk verstorende factoren. De hoogste risicocijfers worden gevonden voor de definities van hyperoxie gebaseerd op gemiddelde of mediane zuurstofwaarden berekend over de opnameduur. Daarnaast hebben we aangetoond dat de kans op ziekenhuissterfte lineair toeneemt met de tijdsduur waarbij er sprake is van hyperoxie bij een IC patiënt. Dit brengt ons tot de conclusie dat zorgverleners de zuurstofwaarden van kritisch zieke patiënten binnen veilige marges moeten houden, zoals we dat ook al voor veel andere variabelen nastreven.

In het derde en laatste deel van dit proefschrift hebben we onderzoek gedaan naar de huidige omgangsvormen met zuurstoftherapie en naar strategieën om de naleving van richtlijnen te bevorderen. Daartoe hebben we zelf-gerapporteerde ideeën en standpunten van IC artsen en verpleegkundigen ten aanzien van zuurstoftherapie en –streefwaarden in kaart gebracht en vergeleken met hun daadwerkelijke gedrag en behandelingsstrategieën in drie grote intensive

care units in Nederland (**hoofdstuk 8**). De meeste IC zorgverleners erkennen het potentiële gevaar van langdurige blootstelling aan hyperoxie en rapporteren een lage tolerantie voor hoge zuurstofwaarden. In de klinische praktijk blijkt echter dat een groot gedeelte van de door hen behandelde patiënten bloot gesteld wordt aan hogere zuurstofwaarden in het slagaderlijke bloed dan de streefwaarden die de zorgverleners zelf hebben benoemd.

Als vervolg op deze observaties, hebben we de haalbaarheid, effectiviteit en klinische uitkomsten bestudeerd van implementatie van nieuwe zuurstofstreefwaarden (**hoofdstuk 9**). Op de drie betrokken Nederlandse IC afdelingen werd hiervoor een richtlijn geïmplementeerd waarbij conservatieve oxygenatie werd nagestreefd met een streefwaarde van 55-86 mmHg (7.3-11.5 kPa) voor arteriële zuurstofspanning (PaO_2) en 92-95% voor de zuurstofsaturatie van het bloed. In het eerste jaar bestond de implementatie uit het geven van onderwijs en verspreiden van zakkaartjes en posters. In de tweede fase werd een geautomatiseerd behandeladvies gegeven wanneer de zuurstofwaarde van de patiënt buiten de streefwaarden viel. Beide fases werden vergeleken met de periode voorafgaand aan de implementatie. Het blijkt goed haalbaar om dit beleid te implementeren en te handhaven op de afdelingen. Er wordt snel effect gezien van het onderwijs en de trainingen op de behaalde zuurstofwaarden in het bloed van de patiënten in de deelnemende centra. Een conservatief zuurstofbeleid voor IC patiënten blijkt op basis van deze studie haalbaar en veilig, maar voor het aantonen van effect op klinische uitkomsten is de opzet van deze studie niet afdoende en zullen nieuwe gerandomiseerde studies nodig zijn. De behandelparadigma's 'treat first what kills first' en 'the more, the merrier' leiden vaak tot ruimhartige zuurstoftoediening om een tekort aan zuurstof (hypoxie) te vermijden, maar er zal bij de kritisch zieke patiënt ook aandacht moeten worden besteed aan het vermijden van hyperoxie en zuurstofvergiftiging.

CURRICULUM VITAE

Hendrik Helmerhorst was born in Amsterdam, on the 26th of May 1986. He graduated cum laude from Grammar School (St. Ignatius Gymnasium, Amsterdam) in 2004. In that same year, he started Medical School at the Academic Medical Center, University of Amsterdam. In 2009 he started a research fellowship at the Medical Research Council – Epidemiology Unit from the University of Cambridge. After his graduation in June 2012, he started working as a research physician at the department of Intensive Care of the Leiden University Medical Center in Leiden and the Laboratory of Experimental Intensive Care and Anesthesiology (LEICA), Academic Medical Center in Amsterdam. The research described in this thesis was performed in this period. In 2015 he was rewarded the 'Young Investigator Award' from the European Society of Intensive Care Medicine for his ongoing and planned research projects on the effects of hyperoxia in critical illness. In April 2016 he started as a resident (AIOS) at the Anesthesiology department of the Leiden University Medical Center.

PORTFOLIO

PhD Training	Year
Courses	
Laboratory Animal Science – ethics and experimentation (LUMC)	2012
BROK – Good Clinical Practice (Boerhaave CME)	2013
Medical Business Masterclass 1 (Stichting Medical Business)	2013
Medical Business Masterclass 2 (Stichting Medical Business)	2014
Laboratory Safety and Environment (AMC)	2014
R Statistics Basic (Boerhaave CME)	2014
R Statistics Advanced (Boerhaave CME)	2014
Statistics in Medicine (Stanford University)	2014
Clinical Epidemiology (Boerhaave CME)	2015
Regression Analysis (Boerhaave CME)	2015
Repeated Measurements (Boerhaave CME)	2015
Presentations and conferences	
Beliefs and actual practice of oxygen therapy in the ICU (*poster presentation*, 33rd ISICEM, Brussels, Belgium)	2013
The impact of $PaCO_2$ and PaO_2 on hospital mortality after cardiac arrest (*oral presentation*, 27th ESICM Congress, Barcelona, Spain)	2014
Out-of-hospital cardiac arrest and arterial carbon dioxide (*oral presentation*, NICE discussion meeting, Nieuwegein, The Netherlands)	2014
The immune response after prolonged hyperoxic mechanical ventilation (*poster presentation*, 35th ISICEM, Brussels, Belgium)	2015
Stepwise implementation is effective in lowering oxygenation targets (*poster presentation*, ATS International Conference, Denver, USA)	2015
Oxygen toxicity and target ranges: too little, too much and enough (*oral presentation*, Venticare Congress, Utrecht, The Netherlands)	2015
Metrics of arterial hyperoxia and associated outcome in critical care (*oral presentation*, 28th ESICM Congress, Berlin, Germany)	2015
Improved adherence to lower oxygenation targets by a stepwise implementation strategy (*oral presentation*, NVIC Congress, 's Hertogenbosch, the Netherlands)	2015
Pathophysiology of hyperoxia and guidelines for oxygen therapy (*oral presentation*, Regional Lecturing Symposium, Leiden, The Netherlands)	2015
More or less oxygen in the ICU (*oral presentation*, Topics in IC, Lunteren, The Netherlands)	2016
Research meetings	
Intensive Care Research Meeting, LUMC (monthly)	2013-2016
Intensive Care Research Meeting, AMC (weekly)	2012-2015
Intensive Care Journal Club, AMC (monthly)	2012-2015
Laboratory of Experimental Intensive Care and Anesthesiology Meeting, AMC (weekly)	2012-2015
Peer review activities	
Annals of Intensive Care	2015-2017
Intensive Care Medicine	2014-2015
Journal of Travel Medicine	2014-2015
Parameters of Esteem	
Young Investigator Award, European Society of Intensive Care Medicine	2015

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1. **Helmerhorst HJ**, Schouten LR, Wagenaar GT, Juffermans NP, Roelofs JJ, Schultz MJ, de Jonge E, van Westerloo DJ. Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. *Intensive Care Medicine Experimental*. 2017 May;5(1):27.

2. de Wilde RB, **Helmerhorst HJ**, van Westerloo DJ. Cerebral blood flow velocity during chest compressions in cardiac arrest. *Netherlands Journal of Critical Care*. 2017 July;25(4):137-139.

3. **Helmerhorst HJ**, de Wilde RB, Lee DH, Palmen M, Jansen JR, van Westerloo DJ, de Jonge E. Hemodynamic effects of short-term hyperoxia after coronary artery bypass grafting. *Annals of Intensive Care*. 2017 Feb;7(1):20.

4. **Helmerhorst HJ**. Zuurstofsaturatie. *Nurse Academy*. 2017;1:58-62.

5. **Helmerhorst HJ**, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, van Westerloo DJ. Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care. *Critical Care Medicine*. 2017 Feb;45(2):187-195.

6. **Helmerhorst HJ**, van Westerloo DJ, de Jonge E. The authors reply. *Critical Care Medicine*. 2016 Oct;44(10):e1016.

7. Schouten LR, **Helmerhorst HJ**, Wagenaar GT, Haltenhof T, Lutter R, Roelofs JJ, van Woensel JB, van Kaam AH, Bos AP, Schultz MJ, Walther T, Wösten-van Asperen RM. Age-Dependent Changes in the Pulmonary Renin-Angiotensin System Are Associated With Severity of Lung Injury in a Model of Acute Lung Injury in Rats. *Critical Care Medicine*. 2016 Dec;44(12):e1226-e1235.

8. **Helmerhorst HJ**, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Wilde RBP, van den Akker-van Marle ME, van Bodegom-Vos L, de Vries M, Eslami S, de Keizer NF, Abu-Hanna A, van Westerloo DJ, de Jonge E. Effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in critically ill patients: a before and after trial. *Critical Care Medicine*. 2016 Mar; 44(3):554-63.

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11. **Helmerhorst HJ**, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. *Critical Care*. 2015 Aug;19:284.

12. **Helmerhorst HJ**, Roos-Blom M-J, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis and meta-regression of cohort studies. *Critical Care Medicine*. 2015 Jul;43(7):1508-1519.

13. **Helmerhorst HJ**, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, van Westerloo DJ. Self-reported attitudes versus actual practice of oxygen therapy by ICU nurses and physicians. *Annals of Intensive Care*. 2014 Jul; 4:23.

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