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PREFACE

The work reported in this PhD thesis has been conducted during my position as a PhD student at the Department of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, from December 2015 to April 2019, in collaboration with the Centre for Research in Intensive Care (CRIC), Copenhagen, Denmark.

Several persons have made the conductance of this PhD study possible. First, I would like to thank my main supervisor Professor Bodil Steen Rasmussen; I am very grateful for being granted the possibility to conduct my PhD study, and for being given the opportunity to be the coordinating investigator of the Handling Oxygenation in the Intensive Care Unit (HOT-ICU) trial. Thanks for support throughout the PhD process, for scientific guidance and interesting discussions, and for encouraging and enabling me to continue my scientific career.

I also wish to thank my assistant supervisor Professor Anders Perner, and the remaining Management Committee of the HOT-ICU trial, Jørn Wetterslev and Theis Lange, for scientific aid, guidance, and constructive criticism.

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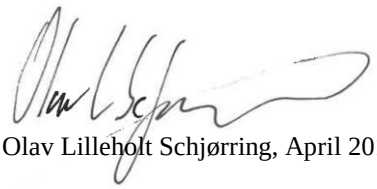
and collaboratively conducting the systematic reviews needed ahead of the HOT-ICU trial.

A large thank you also goes out to the primary national investigators and local site investigators of the HOT-ICU trial, for always warmly welcoming me, and for being friendly and open towards the trial in all of my investigator visits.

Also thanks to the Innovation Fund Denmark for granting the financial support for my PhD study.

Finally, my utmost thanks go to my amazing wife Louise, who has supported me throughout the PhD process, for sparing with me and disburdening me of my frustrations, for taking care of our children when I was not present - and for the way that your mind works, which are inspiring and always makes me see things in a new perspective.



Olav Lilleholt Schjørring, April 2019

LIST OF PAPERS

This PhD thesis is based on the following papers:

I. Schjørring O.L, Toft-Petersen A.P, Kusk K.H, Mouncey P, Sørensen E.E, Berezowicz P, Bestle M.H, Bülow H-H, Bundgaard H, Christensen S, Iversen S.A, Kirkeby-Garstad I, Krarup K.B, Kruse M, Laake J.H, Liboriussen L, Laebel R.L, Okkonen M, Poulsen L.M, Russell L, Sjövall F, Sunde K, Søreide E, Waldau T, Walli A.R, Perner A, Wetterslev J, Rasmussen BS; **Intensive care doctors' preferences for arterial oxygen tension levels in mechanically ventilated patients**; Acta Anaesthesiol Scand. 2018 Nov;62(10):1443-1451. doi: 10.1111/aas.13171. Epub 2018 Jun 21
(Appendix A)

II. Schjørring O.L, Jensen A.K.G, Nielsen C.G, Ciubotariu A, Perner A, Wetterslev J, Lange T, Rasmussen B.S; **Arterial oxygen tensions in mechanically ventilated patients in the intensive care unit**: **a descriptive study of hyperoxaemia and associations with mortality.** Article draft, submitted to Intensive Care Medicine on April 17, 2019
(Appendix B)

III. Schjørring O.L, Perner A, Wetterslev J, Lange T, Keus F, Laake J.H, Okkonen M, Siegemund M, Morgan M, Thormar K.M, Rasmussen B.S, and the HOT-ICU Investigators; **Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) - Protocol for a randomised clinical trial comparing a lower vs a higher oxygenation target in adults with acute hypoxaemic respiratory failure**; Acta Anaesthesiol Scand. 2019 Mar 18. doi: 10.1111/aas.13356. [Epub ahead of print]
(Appendix C)

IV. Schjørring O.L, Rasmussen B.S; **The paramount parameter: arterial oxygen tension versus arterial oxygen saturation as target in trials on oxygenation in intensive care**; Crit Care. 2018 Nov 22;22(1):324. doi: 10.1186/s13054-018-2257-9
(Appendix D)

ENGLISH SUMMARY

Oxygen supplementation is an essential part of the treatment of hypoxaemic respiratory failure in the intensive care unit (ICU). However, the fear of evidently harmful hypoxia has led to a liberal oxygenation practice, and so large proportions of patients admitted to the ICU have arterial oxygen tension (PaO_2) levels above the normal physiological range despite fractions of inspired oxygen (FiO_2) several times above the atmospheric content. This may not be opportune, since several well-defined adverse reactions to excessive oxygen supplementation exist and associations between hyperoxaemia and increased mortality have been established in numerous acutely ill subgroups of patients, including ICU patients overall. The optimal oxygenation level however, balancing harms from hypoxaemia and hyperoxaemia alike, remains essentially unknown.

This PhD thesis revolves around the initiation of a large, randomised clinical trial on higher versus lower oxygenation targets in patients acutely admitted to the ICU with hypoxaemic respiratory failure, the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial. The thesis contains the preparative studies conducted being a survey aiming to clarify ICU doctors' preferences and attitudes towards oxygen supplementation in mechanically ventilated patients, and an observational study of patients admitted to five ICUs in the North Denmark Region, aiming to clarify the current clinical practice of oxygen supplementation in the ICU, and to investigate associations between PaO_2 levels and mortality. Finally the thesis contains the published protocol for the HOT-ICU trial, an update on the current trial status, and an editorial specifically addressing the choice of PaO_2 as target parameter in the trial.

In the oxygenation survey, we established that most ICU doctors' preferred the PaO_2 to the arterial oxygen saturation as parameter when evaluating oxygenation, that the PaO_2 levels generally preferred ranged from 8 kPa to 12 kPa depending on the specific patient category, and that the HOT-ICU oxygenation targets of 8 kPa and 12 kPa, respectively, were generally judged as within the acceptable range of a clinical trial.

In the observational study, we found that the median PaO_2 levels were very close to the 12 kPa HOT-ICU control group, that the oxygenation levels did not depend on whether a patient received mechanically ventilation, and that despite overall reductions in FiO_2 in response to hyperoxaemia, hyperoxaemia remained frequent and was associated with increased ICU mortality.

The HOT-ICU trial was initiated in June 2017, and is currently running in five European countries with 1,639 of 2,928 patients included so far. The results of the HOT-ICU trial will hopefully add a small piece of evidence to the puzzle of the optimal oxygenation level in patients admitted to the ICU, enabling a more evidence based future approach to oxygen supplementation here.

DANSK RESUMÉ

Brugen af ilttilskud er en nødvendig del af behandlingen af patienter med lungesvigt indlagt på intensivafdeling. Frygten for evident skadelig iltmangel har imidlertid ført til en særdeles liberal ilttilskudspraksis, hvor en stor del af intensivpatienterne har arterielle ilttensioner (PaO_2), der ligger over normalområdet for baggrundsbefolkningen, og dette på trods af iltfraktioner i indåndingsluften (FiO_2) der er flere gange iltindholdet i atmosfæren. Denne praksis er måske ikke hensigtsmæssig, da høj FiO_2 medfører flere veldefinerede bivirkninger, og høj PaO_2 er påvist associeret med en øget dødelighed blandt flere undergrupper af kritisk syge patienter, herunder patienter indlagt på intensivafdeling. Det optimale PaO_2-niveau, der afvejer risikoen for iltmangel i forhold til risikoen for bivirkninger ved iltbehandlingen, kendes imidlertid ikke.

Afhandlingens omdrejningspunkt er igangsættelsen af et stort klinisk lodtrækningsforsøg, Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU), der undersøger højere versus lavere PaO_2 i blodet hos akutindlagte patienter på intensivafdeling med lungesvigt. Afhandlingen indeholder de forberedende studier til forsøget, hvilket indbefatter en spørgeskemaundersøgelse til afklaring af intensivlægers præferencer og holdninger i forhold til ilttilskud til respiratorbehandlede patienter, samt et observationelt studie af patienter indlagt på fem intensivafdelinger i Region Nordjylland, hvis formål det var at klarlægge den nuværende kliniske praksis på området, samt at undersøge sammenhængen mellem høj PaO_2 og dødelighed. Slutteligt, så indeholder afhandlingen den publicerede protokolartikel for HOT-ICU-forsøget, den nuværende forsøgsstatus, og en leder-artikel der argumenterer for valget af PaO_2 som iltningsparameter i forsøget.

I spørgeskemaundersøgelsen fandt vi, at flest læger foretrak PaO_2 frem for den arterielle iltmætning som parameter, når de skulle vurdere iltningsniveauer. Endvidere afklarede vi, at de foretrukne PaO_2-niveauer lå fra 8 kPa til 12 kPa alt afhængigt af patientkategorien, og at HOT-ICU-iltningsmålene på henholdsvis 8 kPa og 12 kPa vurderedes inden for de acceptable iltningsniveauer i et klinisk forsøg.

I det observationelle studie fandt vi, at PaO_2-niveauerne i kohorten overordnet lå meget tæt på kontrolgruppeiltningsmålet på 12 kPa i HOT-ICU-forsøget, at iltningsniveauerne var uafhængige af brugen af respiratorbehandling, og at selvom der generelt blev reduceret i ilttilskud ved for høje iltningsniveauer, så var overdreven iltning i blodet hyppig og koblet til en øget dødelighed på intensivafdeling.

HOT-ICU-forsøget blev igangsat i juni 2017 og pågår i fem europæiske lande, aktuelt er 1.639 af 2.928 patienter inkluderet. Forsøget vil bidrage med en smule evidens, på et område hvor dette er hårdt tiltrængt, og vil derved fremadrettet være med til at sikre en mere evidensbaseret og hensigtsmæssig brug af ilttilskud på intensivafdeling.

ABBREVIATIONS

ABG: arterial blood gas

ARDS: acute respiratory distress syndrome

ATP: adenosine triphosphate

AUC: area-under-the-curve

CABG: coronary artery bypass grafting

CI: confidence interval

CO_2: carbon dioxide

COPD: chronic obstructive pulmonary disease

CPAP: continuous positive airway pressure

CPR: civil personal register

DMSC: data monitoring and safety committee

DNA: deoxyribonucleic acid

DRG: diagnosis-related group

ECMO: extracorporeal membrane oxygenation

eCRF: electronic case report form

FiO_2: fraction of inspired oxygen

GOS: Glasgow outcome scale

GRADE: Grading of Recommendations, Assessment, Development and Evaluation

HOT-ICU: Handling Oxygenation Targets in the Intensive Care Unit

ICU: intensive care unit

IQR: interquartile range

mRS: modified Rankin scale

MV: mechanical ventilation

NR: not reported

$PaCO_2$: arterial carbon dioxide tension

PaO_2: arterial oxygen tension

PEEP: positive end-expiratory pressure

ROS: reactive oxygen species

RR: relative risk

SaO_2: arterial oxygen saturation

SAPS II: Simplified Acute Physiology Score II

SD: standard deviation

SpO_2: peripheral oxygen saturation

TWA: time-weighted average

The UK: the United Kingdom

V/Q: ventilation/perfusion

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1. Background

1.1. Introduction

Oxygen is an essential molecule to all human life; it is the prerequisite for oxidative phosphorylation in the mitochondria supplying more than 80% of cellular adenosine triphosphate (ATP) demands[1] and are thus fundamental for bodily energy production. The apparent dangers of hypoxia have been well known since the discovery of oxygen and doctors have strived to avoid these through liberal use of supplemental oxygen. Such liberal practice is still reflected in the observed high proportions of patients with hyperoxaemia[2–12] in intensive care units (ICUs) today. Even though the inherent dangers of hyperoxia are less obvious, the existence of these have likewise been proposed since oxygen was identified; Joseph Priestly, to whom amongst Karl Scheele and Antoine Lavoisier is generally credited the discovery of oxygen, states in the first published paper from 1775 on this new type of air that:

> 'as a candle burns out much faster in dephlogisticated [oxygen enriched] than in common air, so we might, as may be said, live out too fast, and the animal powers be too soon exhausted in this pure kind of air.'[13]

Since then his cautioning has been affirmed as several well established adverse reactions have been shown to be caused by excessive oxygen supplementation.[14–18] Nevertheless, the question remains as to where the balance lies, what is the optimal oxygenation level minimising harm from hypoxia and hyperoxia alike? This PhD thesis pertains to normobaric oxygen therapy in the ICU, and describes the preparative studies conducted, and the planning and initiation of an international multicentre randomised clinical trial, the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial, comparing two separate oxygenation targets in adult patients acutely admitted to the ICU with hypoxaemic respiratory failure.

1.2. Epidemiology of ICU patients

There are approximately 74,000 ICU beds in Europe, representing 2.8% of acute care hospital beds.[19] Patients admitted to the ICU represent the most severely ill proportion of hospital admissions, which is reflected in the high ICU mortality at 16.2% worldwide.[20] As the number of ICU beds per population vary greatly from 3.5 to 24.6 per 100.000 throughout Europe and North America,[19] the illness severity of patients admitted to the ICU also varies as reflected in ICU mortalities ranging from 9.3% in North America to 15.5% in Western Europe,[20] and underlined by the fact that the ICU mortality negatively correlates with the number of ICUs per population.[21] Therefore, the ICU population cannot be regarded as a homogeneous patient population throughout the world. Mortality after discharge from the ICU is similarly high, the in-hospital mortality of ICU patients, ranges from 13.8 to 34.1 worldwide,[20] and the long-

term mortality in ICU patients discharged from hospital remains significantly higher than in the background population for 2 to 5 years following hospital discharge.[22–27] Furthermore, admission to the ICU is associated with significant morbidity in the shape of reduced health-related quality of life,[28,29] increased risk of new chronic condition,[30] post-traumatic stress,[31,32] depression and anxiety,[32] reduced cognitive and neuropsychological function,[33–35] and various negative qualitatively assessed patient related outcomes.[36] Nevertheless, a national Danish cohort study revealed that the chances of returning to work after ICU admission was quite high at 68%;[37] the probability of returning to work was reduced with any life-support given in the ICU, but was not related to number of organ systems supported[37] indicating a somewhat positive outcome for even the most severely ill ICU patients.

ICU admissions represent a significant economic burden to healthcare systems worldwide. Daily costs of ICU admissions have been found to be from €791 to €2025 in Europe,[38–40] and $3250 in the US for non-mechanically ventilated ICU patients and $4772 for patients receiving mechanical ventilation.[41] In addition, healthcare utilisation[42] and healthcare costs[43] after hospital discharge are higher for ICU patients than for non-ICU hospitalisations.

In summary, given that ICU patients have a high mortality and morbidity, and are amongst the most expensive patients in the hospital system, interventions which may improve ICU mortality, reduce morbidity, and/or ICU length-of-stay, may have a significant impact on both patient outcomes as well as on healthcare costs.

1.3. Oxygen toxicity

Even though oxygen is necessary to sustain aerobic life,[1] it is also a well-known fact that oxygen is a highly reactive molecule, and that too much oxygen is directly harmful. Exposure to 90-100% normobaric oxygen will in time inevitably kill all animals, with the exception of amfibians and reptiles[44] at low body temperatures.[16] The survival time however, differs markedly between species; most mammals survive a fraction of inspired oxygen (FiO_2) of 0.90 to 1.00 for 2 to 4 days, whereas primates are specifically resistant to oxygen toxicity with a survival time in monkeys of up to 22 days.[44] Furthermore, the inter-individual survival-time varies greatly with a tendency for younger individuals to survive for longer time than older individuals[44]. Upon exposure to extreme oxygen fractions, animals die in a clinical picture of progressive pulmonary failure initially characterised by inflammation and exudative oedema subsequently followed by consolidation and fibroproliferation,[14–16,44] other findings of more inconsistent certainty are focal haemorrhage, hyalinisation, pulmonary capillary damage, late emphysematous changes, and bronchopneumonia.[16] Exposure of humans to high FiO_2 results in pulmonary changes similar to those found in animals. Studies in human subjects however, are often confounded by underlying pulmonary pathology[45,46] and use of mechanical ventilation,[45–48] which in itself may cause similar pathophysiological changes as oxygen therapy; a problem underlined by

the only controlled interventional pathophysiological autopsy study conducted in humans. In this study brain dead potential organ donors were allocated to an FiO_2 of 0.21 versus an FiO_2 of 1.00 during mechanical ventilation until circulatory death.[47] A decreased pulmonary function in the oxygen group was found, i.e. higher intrapulmonary shunt, higher dead space/tidal volume ratio, and radiologic progression of multiple lobar infiltrations. Autopsies however, revealed similar levels of congestion, atelectasis and oedema formation in both groups, and histologically the lung tissue was indistinguishable between groups.[47]

Several pathophysiological explanations of harmful effects of high FiO_2 and hyperoxaemia exist,[17,18,49] predominantly the increased formation of reactive oxygen species (ROS), the formation of absorption atelectasis, and the occurrence of hyperoxaemic vasoconstriction. In addition, the interaction between hyperoxia and the adverse effects related to mechanical ventilation, and hyperoxia induced hypercapnia in chronic obstructive pulmonary disease (COPD), seem of particular interest when addressing patients admitted to the ICU.

1.3.1. Formation of reactive oxygen species

During oxidative phosphorylation in the mitochondria of aerobic eukaryotic lifeforms a by-product is the formation of ROS.[50,51] ROS include various molecules, all containing a free oxygen radical, i.e. an oxygen atom with one unpaired electron in the outer electron shell. This free radical makes ROS highly reactive, oxidising, and thus possibly damaging, almost any molecule with which they come into contact including proteins, lipids and deoxyribonucleic acids (DNA).[50,51] Relevant biological examples of ROS are the superoxide anion ($O_2^{-}\bullet$), which is the primary ROS and precursor to most other ROS, hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and nitric oxide (NO).[51] Importantly, the production of ROS in the mitochondria is proportionally increased with the intra-mitochondrial oxygen tension,[52] and therefore, the amounts of ROS produced are increased in a linear relationship with the FiO_2 in the lungs, and with the arterial oxygen tension (PaO_2) in the rest of the body, given an unhindered diffusion of oxygen into cells. Under normal conditions continuously produced ROS are balanced by intracellular antioxidants.[14] However, when mitochondrial ROS production increases as a result of increased oxygen supplementation, especially in the lungs were the oxygen tension is the highest, the balance between antioxidants and ROS is tipped and cellular damage occurs. ROS are therefore the primary mediators of pulmonary oxygen toxicity.[16,17,53] In addition, ROS are also produced by bacteria and the neutrophils of the immune system[54] when increased during infection and inflammation, which may accentuate oxygen toxicity in critically ill patients. Nevertheless, high levels of oxygen have been shown to be able to cause inflammation and pulmonary oxygen toxicity, also without the presence of inflammatory cells.[14]

1.3.2. Absorption atelectasis

As FiO_2 is increased, the content of nitrogen in inspired air is consequently reduced. Since oxygen is readily absorbed from the alveoli by blood passing through the pulmonary capillaries, whereas nitrogen remains within the alveoli, the main gas keeping the alveoli open in the end of an expiration is nitrogen. Therefore, the risk of alveolar collapse (absorption atelectasis) increases with higher FiO_2, especially with FiO_2 above 0.60.[55] The formation of absorption atelectasis has been documented thoroughly radiologically in mechanically ventilated patients during general anaesthesia for surgery,[56–59] as well as in patients in the ICU.[60,61] Formation of absorption atelectases decreases the ventilation/perfusion (V/Q) ratio,[56] decreases oxygenation,[58,60] and has been proposed to increase the risk of pneumonia,[62] which has been associated with high PaO_2 levels in the ICU.[63] The clinical impact of absorption atelectasis formation on patient relevant outcomes including mortality in the ICU however, remains unknown, especially since the formation of absorption atelectasis can be negated through the use of higher positive end-expiratory pressure (PEEP) levels, both during anaesthesia[58,64,65] and in the ICU.[60]

1.3.3. Hyperoxaemic vasoconstriction

Hyperoxaemia is known to cause vasoconstriction in vascular beds of all tissues[66] with the exception of the lungs[67] and of the placenta[68], where hypoxaemic vasoconstriction is elicited. The specific cellular mechanisms involved in hyperoxaemic vasoconstriction are not known[69] although ROS seem to be involved as antioxidants prevent hyperoxaemic increase in vascular resistance.[70] The clinical consequences of hyperoxaemic vasoconstriction are reduced microvascular blood flow with potential paradox local tissue hypoxia,[71] and an increase in systemic vascular resistance.[72] Haemodynamically, in addition to the increased afterload, hyperoxaemia causes a reduction in heart rate and consequently a lower cardiac output.[72] Such haemodynamic changes are likely not opportune in ICU patients. Randomised controlled trials have identified increased infarct size in non-hypoxaemic patients with myocardial infarction receiving oxygen supplementation,[71,73,74] and an observational study has indicated delayed cerebral ischaemia upon hyperoxaemia after subarachnoidal haemorrhage.[75] This may indicate paradox cardiac and cerebral tissue hypoxia upon oxygen supplementation due to hyperoxaemic vasoconstriction of collateral arteries supplying tissue in the periphery of the infarcted myocardium and the periphery of the injured brain parenchyma, respectively. The largest randomised oxygen supplementation versus no oxygen supplementation trials in patients with acute coronary syndrome overall,[76] and in patients with acute stroke[77] however, found no differences in myocardial infarct size or post-stroke disability, respectively, or in other clinical outcomes between the intervention groups.

1.3.4. Mechanical ventilation and hyperoxia

The use of positive pressure mechanical ventilation as life support in the ICU elicits several adverse reactions related to the mechanical strain and pressure applied to the pulmonary tissue. These include barotrauma, volutrauma, atelectrauma, biotrauma, and shear strain.[78] Especially patients with acute respiratory distress syndrome (ARDS) are susceptible to the mechanical adverse reactions, as these patients represents the population with the most severely injured lungs, and the highest degree of hypoxaemic respiratory failure in the ICU. The physical adverse reactions to mechanical ventilation are in clinical practice sought minimised through the advantageous use of lung protective ventilation with low tidal volumes,[79] as well as through various open lung strategies with varying success including high PEEP levels,[80] recruitment maneuvers,[81,82] or airway pressure release ventilation,[83] as well as extra corporeal membrane oxygenation (ECMO).[84,85] The pathophysiological changes, which occur after prolonged or excessive positive pressure mechanical ventilation are hard to distinguish from the changes seen after prolonged exposure to high FiO_2.[16] Therefore, it is plausible that high FiO_2 and mechanical ventilation interacts in causing pulmonary damage. That such an interaction occurs has been demonstrated in a number of experimental animal studies, finding a distinct and possibly potentiating effect of high FiO_2 on the pulmonary damages caused by high-stretch mechanical ventilation.[86–92]

1.3.5. Hyperoxia and hypercapnia

In patients with COPD or other chronic pulmonary disease with increased risk of respiratory acidosis and/or habitual hypercapnia, excessive oxygen supplementation may lead to occurrence or aggravation of hypercapnia and respiratory acidosis.[93–96] There are three pathophysiological mechanisms contributing to the development of hyperoxic hypercapnia in this patient population: (1) habitual hypercapnia causing a shift towards a non-hypercapnia-dependant central hypoxic respiratory drive with the consequence that hyperoxaemia causes hypoventilation with a following increase in arterial carbon dioxide tension ($PaCO_2$),[93,97] (2) reversion of hypoxic pulmonary vasoconstriction causing a hypercapnic V/Q mismatch with increased perfusion of the alveolar deadspace,[93,97] and (3) the Haldane effect, a release of carbon dioxide (CO_2) bound to haemoglobin as this is displaced by oxygen.[98] It is a general consensus that the Haldane effect is the least important of these mechanisms,[93,97] estimated to contribute with approximately 25% of the CO_2 increase seen in experimental settings.[99] Whether the reversion of hypoxic vasoconstriction with following V/Q mismatch or central respiratory depression due to hypoxic respiratory drive is the most important mechanism however, is still a matter of debate; most studies conclude that V/Q mismatching represents the primary cause,[99–105] whereas a few well conducted studies support a reduction in minute ventilation due to central respiratory depression as the primary mechanism.[106–108] Studies in invasively[105,109] and in non-invasively[110] mechanically ventilated patients with COPD on a supportive ventilator mode, have

not been able to confirm the occurrence of hyperoxaemic hypercapnia here,[109,110] or has found this to be of minor importance with a mean increase in $PaCO_2$ of 0.4 kPa.[105] This indicates that the risk hypercapnia upon hyperoxaemia may differ in ICU patients as compared to patients in other settings. The lack of hyperoxic hypercapnia during mechanical ventilation points towards V/Q mismatching as the primary cause of the phenomenon, since V/Q mismatching would to some degree be ameliorated by supportive mechanical ventilation, whereas a depression in the central respiratory drive should have just as prominent an effect on hypercapnia in a supportive ventilator mode as in patients not receiving mechanical ventilation. Likely however, hyperoxic hypercapnia in COPD patients is caused by a combination of both mechanisms with minor contribution from the Haldane effect and with high inter-individual variability.

1.4. Hypoxaemia and hypoxia

Hypoxaemia designates a low level of oxygen in the blood, whereas hypoxia designates a condition of insufficient oxygenation in any tissue potentially causing harm due to attenuated oxidative metabolism. Hypoxaemic hypoxia is therefore hypoxaemia to a level where hypoxia in any given tissue occurs.[96] The definitions are complicated however, by the fact that no consensus on the oxygenation level defining hypoxaemia exists; the predominant definition seems to be a PaO_2 below 8 kPa or an SaO_2 below 90%,[96] although one could argue that any oxygenation below the normal physiologic range of a PaO_2 from 10.6 kPa to 13.3 kPa[111] or an SaO_2 of approximately 94% to 98%[96] should be considered hypoxaemic.[96] Or that hypoxaemia should be defined as below the oxygenation levels used in current clinical practice,[112,113] which may be as low as a PaO_2 of 7.3 kPa to 10.7 kPa or an SaO_2 of 88% to 95%, since this is targeted in patients with ARDS[79,80] and has been proposed as the optimal target level for critically ill patients overall.[49,114,115] In any case, hypoxaemia is prevalent in patients admitted to the ICU and can be caused by several mechanisms including: hypoventilation, V/Q mismatching (to some degree ameliorated by physiological hypoxic pulmonary vasoconstriction), intrapulmonary right-to-left shunting (essentially a localised V/Q ratio of 0), and diffusion impairment.[96,116]

The tolerated levels of hypoxaemia in humans varies extensively depending on the overall condition of the body; i.e. the ability compensate for a lower oxygenation on the short-term through increased oxygen delivery by haemodynamic adaptations, and on the long-term through adaptation to chronic hypoxaemia individually and through adaptation to generational hypoxaemia in populations on an evolutionary scale, as seen in highlanders of the Andes and the Himalayas.[112] The ability of the body to adapt to sustained hypoxaemia is remarkable, which is exemplified in the lowest registered PaO_2 of 2.5 kPa and SaO_2 of 34.4% known to be measured in a healthy person, obtained in an altitude of 8,400 meters at mount Everest after 20 minutes without oxygen supplementation.[117] A similar level of acute extreme hypoxaemia however, is not tolerated in non-adapted individuals; overall, negative effects on cognition of acute hypoxaemia indicating insufficient cerebral oxygenation in healthy adults

occurs at a PaO_2 below 8 kPa,[118] and a study of induced acute hypoxaemia in healthy adults found that at SaO_2 levels around 80% neurocognitive functions were markedly impaired.[119] Interestingly, the participants exposed to acute hypoxaemia in this study did not feel worried, and none of them removed their masks during the 90 minutes intervention period, despite severe cognitive failure and several negative perceptual experiences including tiredness, light-headedness, dizziness, headaces, irritability and restlessness.[119] This is consistent with other experimental findings showing that in healthy adults no sensation of air hunger upon hypoxaemia occurs when the increased respiratory drive can be met (with lowering of $PaCO_2$). Whereas during restricted breathing where normocapnia is kept, air hunger to hypoxaemia arises in a hyperbolar manner with a sudden increase at PaO_2 below 6.7 kPa. This observation seems relevant when evaluating patients with subjective air hunger in the clinical setting.[120] In comparison, hypercapnia elicits air hunger sensation in a linier manner irrespective of increased minute ventilation if this does not reduce the $PaCO_2$,[120] and so, the $PaCO_2$ level can be considered the primary moderating parameter of subjective dyspnoea. Neither the short-term capacity for haemodynamic compensation nor the long-term adaptations, which may compensate for hypoxaemia are usually present in acute critically ill patients. Therefore, failure of oxygen delivery and tissue hypoxia will presumably be evident at much less pronounced levels of hypoxaemia that in healthy individuals, also in spite of many ICU patients to some degree being adapted to subacute, sustained, or chronic hypoxaemia due to the duration of current critical illness leading to the ICU admission, or to the presence of chronic pulmonary disease.[112] Importantly, even though oxygen delivery is hampered by hypoxaemia, the opposite is not the case; oxygen delivery will not be increased above normal by excessive oxygen supplementation and hyperoxaemia.[72] Essentially, as only global oxygenation can be measured directly with any certainty in clinical practice, and as plasma lactate, and mixed and central venous oxygen saturations, which are the primary indicators of local tissue hypoxia, may be severely confounded by haemodynamic changes,[121] the specific PaO_2 or SaO_2 where local tissue oxidative metabolism fails in the individual patient is hard to evaluate.

1.5. Oxygenation practices in ICUs

A considerable number observational studies of oxygenation levels in adult patients admitted to the ICU have been conducted in various subgroups as well as in overall cohorts. An overview of the studies addressing ICU patients overall, ICU patients with sepsis, and specifically mechanically ventilated ICU patients and relevant subgroups of these are presented in Table 1. In general oxygenation levels during mechanical ventilation in the ICU are found to be liberal with mean and median PaO_2 levels ranging from 12.4 kPa[2] to 21.2 kPa[4] and SaO_2 or peripheral oxygen saturation (SpO_2) levels around 97-98%.[6,10,11,122] A similar overview of preferences related to oxygen supplementation in the ICU from surveys of ICU physicians and nurses can be found in Table 2. Overall preferences of oxygenation is generally judged to be more

restrictive than the actual oxygenation levels found in observational studies. With ICU doctors[123] being less worried about hypoxaemia than ICU nurses.[124]

Author, publication year	Country	Design (duration of exposure)	n	Mean/median oxygenation	Conclusions
ICU overall					
Parke, 2013[125]	Australia and New Zealand	Prospective cross-sectional (24 hours)	506 (108 with ABG)	Highest PaO_2: 17.2 kPa (SD 12.5 kPa), Lowest PaO_2: 11.7 kPa (SD 12.5 kPa)	Generally, oxygen therapy was poorly prescribed and prescriptions did not meet standard recommendations
Helmerhorst, 2017[9]	The Netherlands	Retrospective cohort (ICU stay)	14,441	PaO_2: 10.8 kPa (IQR 9.3-13.1 kPa)	Severe hyperoxaemia (PaO_2 > 26.6 kPa) was associated with increased mortality in most of the metrics assessed
Ruggiu, 2018[126]	France	Retrospective cohort (ICU stay)	130	NR	≥ one episode of hyperoxaemia (> 13.3 kPa) during ICU stay was associated with increased ICU mortality
Ebmeier, 2018[127]	Australia and New Zealand	Prospective cohort (one ABG pr. patient)	394	PaO_2: 11.3 kPa (SD 2.8 kPa), SaO_2: 95.7% (SD 2.7%)	Comparison between SpO_2 and SaO_2, findings indicated a risk of unappriciated desaturation occuring when targeting relatively low SpO_2 levels
Sepsis					
Dahl, 2015[128]	Denmark, Sweden, Norway, Finland, Iceland	Post-hoc analysis of conducted RCTs (first five ICU days)	1,770	Median PaO_2: 9.8 kPa (5-95% range: 6.4-19.9 kPa)	No associations between hyperoxaemia and increased 90-day mortality were found
Zhang, 2016[8]	USA	Retrospective cohort (ICU stay)	11,002	23.0 kPa (SD 16.6 kPa)	Increasing PaO_2 levels > 40 kPa was associated with parabolic increase in in-hospital mortality

Mechanical ventilation					
De Jonge, 2008[2]	The Netherlands	Retrospective cohort (24 hours, ICU stay in a subset)	36,307 (3,322 for entire ICU stay)	24 h PaO_2: 13.2 kPa (SD 6.5 kPa), ICU stay PaO_2: 12.4 kPa (SD 5.5 kPa)	All levels of hyperoxaemia (from > 10.6 kPa to ≥ 16.4 kPa) were associated with increased ICU mortality in the 24-hour cohort. Hyperoxaemia in entire ICU-stay cohort however, was not
De Graaff, 2011[3]	The Netherlands	Retrospective cohort (ICU stay)	5,498	NR	22% of ABGs had hyperoxaemia (PaO_2 > 16 kPa), in only 25% of these was the FiO_2 subsequently decreased
Eastwood, 2012[5]	Australia and New Zealand	Retrospective cohort (24 hours)	152,680	'Worst' PaO_2[a]: 20.3 kPa (SD 14.6 kPa)	Hyperoxaemia (> 16 kPa) in 24-hour 'worst' PaO_2[a] after ICU admission was not associated with increased mortality
Suzuki, 2013[6]	Australia	Prospective cohort	51	TWA PaO_2: 14.3 kPa (IQR 12.5-17.5 kPa), TWA SaO_2: 97.7% (IQR 96.6-98.5%)	Excess O_2 delivery was common, a median of 59% (IQR 29-83) of the time was spent in hyperoxaemia (SpO_2 > 98%)
Guedes, 2013[129]	Brazil	Prospective cross-sectional (72 hours)	48	PaO_2: 16.7 kPa (SD 2.7 kPa)	PaO_2 was proportionally higher than their calculated 'ideal' PaO_2 based on their age
Panwar, 2013[122]	Australia	Retrospective cohort (7 days)	101	TWA SpO_2: 97.1% (95% CI 96.8-97.4%)	TWA PaO_2 were > 10.7 kPa in 80% of MV days
Helmerhorst, 2014[130]	The Netherlands	Retrospective cohort (ICU stay)	5,565	PaO_2: 12.9 kPa (SD 5.1 kPa)	Comparison with questionnaire, 73% of PaO_2 values were > 10.0 kPa (upper limit of overall self-reported acceptable range)
Itagaki, 2015[7]	Japan	Retrospective cohort (duration of MV)	328	PaO_2: 12.0 kPa (IQR 9.9 –14.5 kPa) to 14.0 kPa (IQR 11.7 – 16.0 kPa) during MV	At 48 hours after MV initiation 25% of patients were hyperoxaemic (PaO_2 > 16.0 kPa)

Six, 2016[63]	France	Retrospective cohort (duration of MV)	503	NR	Hyperoxaemia (PaO_2 > 16.0 kPa) at ICU admission, and percentage of days with hyperoxemia were both independently associated with development of ventilator associated pneumonia
Dennis, 2017[10]	Australia	Retrospective cohort (12 hours)	151	PaO_2: 15.6 kPa (SD 4.9 kPa), mean SaO_2: 98% (range 91-100%)	FiO_2 considered below level of oxygen toxicity, floor effect of FiO_2 = 0.30 below with clinicians did not go
Egi, 2018[11]	Japan	Prospective cohort (7 days)	454	Median PaO_2: 12.8 kPa, median SaO_2: 98%	PaO_2 was ≥ 13.3 kPa during 47% of the study period and was ≥ 17.3 kPa during 18% of the study period
Kraft, 2018[12]	Austria	Retrospective cohort (7 days)	419	TWA PaO_2: 14.0 kPa (SD 2.4 kPa)	No association between hypoxaemia (TWA PaO_2 > 16 kPa) and mortality was found
Ramanan, 2018[4]	Australia and New Zealand	Retrospective cohort (24 hours)	219,723	'Worst' PaO_2[a]: 21.2 kPa (SD: 15.0 kPa)	Hyperoxaemia with PaO_2 > 30.0 kPa in 24-hour 'worst' PaO_2[a] after ICU admission was associated with increased mortality
Non-invasive ventilation					
Schernthaner, 2017[131]	Germany	Retrospective cohort (duration of NIV)	475	11.2 kPa (SD 2.6 kPa)	High peak PaO_2 (> 13.0 kPa) was associated with increased in-hospital and long-term mortality

ARDS					
Rachmale, 2012[132]	USA	Retrospective cohort (48 hours)	210	NR	Excessive oxygen exposure (time with FiO_2 > 0.50 and SpO_2 > 92%) was associated with longer MV and ICU stay, however not with increased mortality
Laffey, 2016[133]	50 countries worldwide	Prospective cohort (ARDS onset)	2,377	PaO_2: 12.4 kPa (SD 5.1 kPa)	No associations between PaO_2 at ARDS onset and in-hospital mortality was found
Aggarwal, 2018[134]	USA	Post-hoc analysis of conducted RCTs (duration of MV)	2,994	NR	Cumulative PaO_2 > 10.7 kPa with FiO_2 > 0.50 was associated with increased 90-day mortality

Table 1 Observational studies of oxygenation levels in ICU patients overall, in ICU patients with sepsis, and specifically in mechanically ventilated ICU patients and relevant subgroups of these. ICU: intensive care unit; ABG: arterial blood gas; PaO_2: arterial oxygen tension; SD: standard deviation; IQR: interquartile range; NR: not reported; SaO_2: arterial oxygen saturation; SpO_2: peripheral oxygen saturation; USA: United States of America; RCT: randomised clinical trial; FiO_2: fraction of inspired oxygen; TWA: time-weighted average; MV: mechanical ventilation; NIV: non-invasive ventilation; ARDS: acute respiratory distress syndrome. Only studies addressing overall mean or median oxygenation levels (PaO_2, SaO_2, or SpO_2) or associations between hyperoxaemia and clinical outcomes are included. The search strategy used is specified elsewhere.[135] [a]'Worst' PaO_2 was defined as: PaO_2 associated with the highest alveolar-arterial gradient (FiO_2/PaO_2) if FiO_2 > 0.50, and the measured lowest PaO_2 if FiO_2 < 0.50

Author, year	Country	Design	Population	Respondents/ distributed	Assessments	Conclusions
Mao, 1999[136]	Canada	Postal questionnaire analysis	ICU medical directors (doctors)	48/52	Preferences of FiO_2 in relation to SaO_2	Considerable variation found, preferred oxygenation of SaO_2 = 90-95% at FiO_2 = 0.21-0.50, and SaO_2 = 85-90% at FiO_2 = 0.60-1.00
Eastwood, 2011[123]	Australia and New Zealand	Electronic questionnaire analysis	ICU doctors	99/164	Preferences of SaO_2 levels and practices related to oxygen administration	Most respondents were not concerned of an SaO_2 of 90%, and 57% would accept an SaO_2 of 85-90% for 24-48 hours in a stable patient
Eastwood, 2012[124]	Australia	Electronic questionnaire analysis	ICU nurses	542/1523	Preferences regarding management of oxygen supplementation and SpO_2	More than 60% of respondents would not accept an SpO_2 of 90% for > 1 hour
Eastwood, 2014[137]	Australia	Electronic questionnaire analysis	ICU nurses and doctors	90/162	Preferences of a conservative oxygenation strategy (SpO_2 = 90-92%)	The already implemented conservative oxygenation strategy was readily accepted, 90% of respondents desired to continue this strategy

Helmerhorst, 2014[130]	The Netherlands	Electronic questionnaire analysis	ICU nurses and doctors	215/approx. 500	Preferences of FiO_2 in relation to SaO_2 and PaO_2, compared with actual PaO_2 levels	Preferred SaO_2 and PaO_2 levels were 85-95% and 7-10 kPa, respectively, 73% of PaO_2 values observed were > 10 kPa.

Table 2 Surveys of ICU doctors' and nurses' preferences related to oxygen supplementation in adult ICUs. ICU: Intensive Care Unit; FiO_2: fraction of inspired oxygen; SaO_2: arterial oxygen saturation; SpO_2: peripheral oxygen saturation; PaO_2: arterial oxygen tension. Surveys only addressing general knowledge on oxygenation and/or function of oxygen supplementation devises or pulse oximeters, with no relation to oxygenation targets or level of oxygen supplementation are not included. See Appendix E for full search string, search updated March 2019

1.6. Oxygenation levels associated with mortality in the ICU

Mortality associations with hyperoxaemia in various subgroups of ICU patients have been extensively investigated as seen in Table 1. Several recent metaanalyses have pooled the observational data identifying associations between hyperoxaemia and increased mortality in the ICU overall,[138–140] and in the following ICU subgroups: post-resuscitation from cardiac arrest,[138–142] ischaemic stroke,[138,139] intracranial haemorrhage,[139] and during ECMO treatment.[140] In addition, oxygen exposure above 10.7 kPa with FiO_2 above 0.50 has been associated with increased mortality in ARDS,[134] and hyperoxaemia has been associated with increased risk of ventilator associated pneumonia in the ICU.[63] A general limitation of the observational association studies however is, that very few of these studies investigate oxygenation levels in the ICU beyond the first 24 hours, and most studies do not include all arterial blood gas (ABG) analyses conducted in the inclusion period (see Table 1). Accordingly, the associations found do not necessarily confer to the cumulated oxygen exposure over the entire duration of the ICU admission, which therefore remains unclear. Hypoxaemia has similarly been associated with increased mortality in ICU populations,[2,8,12,128] and hypoxaemia in the ICU has been associated with reduced cognitive function and psychiatric morbidity 12 months after ICU admission with ARDS.[143]

1.7. Interventional trials on oxygenation levels in the ICU

Throughout the last two decades, several interventional trials have been published on higher versus lower oxygenation levels in the ICU, most of these are feasibility trials in subpopulations[144–150] or before-and-after trials[151,152], but larger randomised clinical trials with higher statistical power have also been conducted.[153,154] Table 3 includes all published interventional trials in the ICU on the subject. Furthermore several upcoming, ongoing and unpublished trials on the subject are specified in Table 4.

No recent systematic reviews on randomised clinical trials of higher versus lower oxygenation levels specifically in the ICU have been conducted, a Cochrane systematic review from 2014 identified no relevant trials in mechanically ventilated ICU patients at that time.[113] A recent metaanalysis of randomised clinical trials in acutely ill patients overall however, established an increased mortality with liberal oxygenation strategies as compared with restrictive oxygenation strategies, including trials in ICU patients amongst trials in other acutely ill patient populations (e.g. acute coronary syndrome and stroke).[155] The conclusion of the analysis, and especially the suggested maximum oxygenation level of an SpO_2 of 96% over which oxygen supplementation might become unfavourable however, may be too definitive when considering the large heterogeneity of the included trials, and the vastly differentiated oxygenation strategies used.[156,157] In summary, even though increasing evidence points towards harm from definitive hyperoxaemia with oxygenation levels above the

normal physiological range, the optimal oxygenation targets in the ICU, balancing the risks of hyperoxaemia as well as of hypoxaemia, remain essentially unknown.

Author, year	Country	Design	Population	n	Targets	Results
Gomersall, 2002[144]	Hong Kong	RCT	COPD exacerbation	38	PaO_2 > 9.0 kPa vs PaO_2 > 6.6 kPa	No differences in clinical outcomes
Suzuki, 2014[151]	Australia	Before/after	ICU overall	105	Conventional treatment vs SpO_2 = 90-92%	No mortality difference, reduced incidence of new organ failure in low oxygenation group
Mazdeh, 2015[145]	Iran	RCT	Stroke	51	FiO_2 = 0.50 (Venturi mask) vs no oxygen	No mortality difference, reduced disability at 6 months (mRS) in high oxygenation group
Helmerhorst, 2016[152]	The Netherlands	Before/after	ICU overall	15,045	Conventional treatment vs PaO_2 = 7.3-11.5 kPa and SpO_2 = 92-95%	Reduced hospital mortality and duration of mechanical ventilation in low oxygenation group
Panwar, 2016[146]	Australia, New Zealand, and France	RCT	Invasively mechanically ventilated	103	$SpO_2 \geq 96\%$ vs SpO_2 = 88-92%	No differences in clinical outcomes
Girardis, 2016[153]	Italy	RCT	ICU overall	480	$SpO_2 \geq 97\%$, $FiO_2 \geq 0.40$, and $PaO_2 \leq 20$ kPa vs PaO_2 = 9.3-13.3 kPa, or SpO_2 = 95-98%	Reduced ICU mortality (RR: 0.57, 95% CI: 0.37-0.90) and reduced incidence of shock, liver failure, and bacteraemia in low oxygenation group
Taher, 2016[147]	Iran	RCT	Traumatic brain injury	68	FiO_2 = 0.80 vs FiO_2 = 0.50	Reduced disability at 6 months (GOS, Bartel index and mRS) in high oxygenation group

Smit, 2016[148]	The Netherlands	RCT	Elective CABG (per- and post-operatively)		In the ICU: 17.3-20.0 kPa vs 10.6-13.3 kPa	No differences in clinical outcomes
Asfar, 2017[154]	France	Bi-factorial RCT[a]	Septic shock and invasively mechanically ventilated	442	FiO_2 = 1.00 vs SaO_2 = 88-95%	No mortality difference, reduced incidence of atelectasis and ICU-acquired weakness in low oxygenation group
Young, 2017[158]	Australia, New Zealand	RCT	Invasively mechanically ventilated	100	Conventional practice (with FiO_2 < 0.3 being discouraged) vs SpO_2 = 91-96% (or lower at clinicians' discretion)	Not available[b]
Lång, 2018[149]	Finland	RCT	Traumatic brain injury	65	FiO_2 = 0.70 vs FiO_2 = 0.40	No mortality difference, reduced ICU length-of-stay in high oxygenation group
Jakkula, 2018[150]	Finland, Denmark	Tri-factorial RCT[c]	Post-resuscitation from OHCA	123	PaO_2 = 20-22 kPa vs PaO_2 = 10-15 kPa	No differences in clinical outcomes

Table 3 Interventional trials of higher versus lower oxygenation levels in the intensive care unit. RCT: randomised clinical trial; COPD: chronic obstructive pulmonary disease; PaO_2: arterial oxygen tension; FiO_2: fraction of inspired oxygen; mRS: modified Rankin scale; RR: risk ratio; CI: conficence interval; ICU: intensive care unit; SpO_2: peripheral oxygen saturation; GOS: Glasgow outcome scale; CABG: coronary artery bypass grafting; SaO_2: arterial oxygen saturation; OHCA: out-of-hospital cardiac arrest. The search strategy used is specified elsewhere.[159] [a]Bi-factorial design with hypertonic vs isotonic saline. [b]The intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX), only pilot phase with the first 100 out of 1000 included patients are published with no clinical outcomes reported, the trial has been completed, full results are awaited in Autumn 2019. [c]Tri-factorial design with higher vs lower arterial partial pressure of carbon dioxide targets, and higher vs lower mean arterial pressure targets, respectively.

Trial	Country	Design	Population	Planned inclusion (n)	Targets	Status[a]
ICU-ROX	New Zealand and Australia	RCT	Invasively mechanically ventilated	1,000	Conventional practice (with FiO_2 < 0.3 being discouraged) vs SpO_2 = 91-96% (or lower at clinicians' discretion)	Completed, results are awaited in autumn 2019
LOCO2	France	RCT	ARDS	850	PaO_2 = 12.0-14.0 kPa vs PaO_2 = 7.5-9.3 kPa	Inclusion temporarily stopped after 206 patients, reason for pre-term trial stop awaits
POSDOT	China	RCT	ICU overall	214	SpO_2 96-100% ($FiO_2 \geq 0.30$) vs SpO_2 90-95%	Completed January 2019, results await
HOT-ICU	Denmark, Switzerland, Finland, Norway, the Netherlands, the UK, Iceland	RCT	Hypoxaemic respiratory failure	2,928	PaO_2 = 12 kPa vs PaO_2 = 8 kPa	Recruiting, 1,639 patients included
O2-ICU	The Netherlands	RCT	Sepsis	385	PaO_2 = 16 kPa vs PaO_2 = 10 kPa	Recruiting
TOXYC	The UK	RCT	Invasively mechanically ventilated	60	$SpO_2 \geq 96\%$ vs SpO_2 = 88-92%	Recruiting

BOX	Denmark	Bi-factorial RCT[b]	Post-resuscitation from OHCA	800	PaO_2 = 13-14 kPa vs PaO_2 = 9-10 kPa	Recruiting
ICU-Conservative O2	Italy, Spain, France	RCT	Mechanically ventilated (invasively or non-invasively)	1,000	$SpO_2 \geq 97\%$, $FiO_2 \geq 0.40$, and $PaO_2 \leq 20.0$ kPa vs PaO_2 = 9.3-13.3 kPa, or SpO_2 = 95-98%	Not initiated

Table 4 Completed, ongoing and upcoming randomised clinical trials of higher versus lower oxygenation levels in the intensive care unit. ICU-ROX: Intensive care unit randomised trial comparing two approaches to oxygen therapy; LOCO2: liberal oxygenation versus conservative oxygenation in ARDS; POSDOT: pulse oxygen saturation directed oxygen therapy; HOT-ICU: handling oxygenation targets in the intensive care unit; O2-ICU: optimal oxygenation in the intensive care unit; TOXYC: targeted oxygen therapy in critical illness; BOX: blood pressure and oxygenation targets after OHCA; ICU-conservative O2: conservative vs conventional oxygen administration in critically ill patients. RCT: randomised clinical trial; FiO_2: Fraction of inspired oxygen; SpO_2: peripheral oxygen saturation; ARDS: acute respiratory distress syndrome; PaO_2: arterial oxygen tension; ICU: intensive care unit; UK: United Kingdom; OHCA: out-of-hospital cardiac arrest. [a]Status per April 21, 2019; [b]Bi-factorial design with higher vs lower mean arterial pressure targets.

2. Aims and hypotheses

The overall aims of this PhD thesis were to plan and conduct the preparative studies needed for a pragmatic international multicentre randomised clinical trial of a lower versus a higher oxygenation target in adults acutely admitted to the ICU with hypoxaemic respiratory failure, and to design and initiate such a trial, the HOT-ICU trial.

The overall hypothesis is that a lower oxygenation target compared with a higher oxygenation target will reduce mortality in adults acutely admitted to the ICU with hypoxaemic respiratory failure.

2.1. Substudies

2.1.1. Survey of ICU doctors' preferences for oxygenation levels

The aim of the survey (Paper I) was to quantify a broad segment of Northern European ICU doctors' preferences related to oxygenation levels and to oxygen supplementation in mechanically ventilated adult ICU patients, additionally ensuring that the oxygenation target levels in the HOT-ICU trial would be implementable in clinical practice. We hypothesised that the preferred oxygenation target levels would generally be more restrictive than what observational studies in the ICU indicate.

2.1.2. Observational study on oxygenation levels in the ICU

Analyses of ABG samples from adult patients admitted to five ICUs in two hospitals of the North Denmark Region (Paper II).

Preliminary, we quantified the oxygenation levels in all ABG analyses conducted in the specific ICUs to investigate levels of oxygenation overall (unpublished data), aiming to clarify current clinical practice to establish the control oxygenation target level in the HOT-ICU trial. The overall aim of the final submitted observational study however, was to evaluate the degree of hyperoxaemia, changes in FiO_2 in response to hyperoxaemia, and any associations between hyperoxaemia during invasive mechanical ventilation and mortality in a large cohort of invasively mechanically ventilated adult ICU patients. We hypothesised that large proportions of PaO_2 measurements would be hyperoxaemic, and that hyperoxaemia would be associated with increased all-cause mortality for patients in the ICU and for patients discharged from the ICU, respectively.

2.1.3. The HOT-ICU trial

The aim of the HOT-ICU trial (Paper III) is to compare the effect of a PaO_2 oxygenation target of 8 kPa with a PaO_2 oxygenation target of 12 kPa throughout the duration of the ICU admission including readmissions until a maximum of 90 days, on the 90-day all-cause mortality in acutely admitted adult ICU patients with hypoxaemic respiratory failure. We hypothesise that the lower oxygenation target will reduce the 90-day mortality as compared with the higher oxygenation target.

Additionally, an editorial (Paper IV) is included, the aim of which was to argument for the specific choice of PaO_2 as the oxygenation target parameter in the HOT-ICU trial.

3. Methods

The four papers included in this PhD thesis all revolve around the design of the HOT-ICU trial, consisting of two preparative articles reporting the results of the conducted survey (Paper I) and of the observational study (Paper II), respectively, the protocol article of the HOT-ICU trial (Paper III), and of an editorial arguing specifically for the choice of oxygenation target parameter in the trial (Paper IV). The preparative studies needed to plan the HOT-ICU trial were, apart from the survey and the observational study, systematic reviews on the subject to clarify the overall combined knowledge prior to initiating the trial, as recommended.[160,161] We therefore conducted two systematic reviews with trial sequential analyses on randomised clinical trials of higher versus lower oxygenation levels or levels of oxygen supplementation in ICU patients,[159] and in critically ill patients overall,[135] respectively. Conducted in collaboration with the Copenhagen Trial Unit outside the work of this PhD thesis. Results from both reviews await publication.

3.1. Oxygenation survey (Paper I)

3.1.1. Questionnaire construction and validation

We used a previously validated questionnaire[136] and successive modifications of this[123,130] to construct a questionnaire on preferences for oxygen administration in mechanically ventilated adult ICU patients. Since we specifically wanted to address PaO_2 as target parameter however, which was opposite previously conducted surveys all primarily focusing on SaO_2,[123,130,136] all questions were modified so that they related to the PaO_2, with the exception of the first question where the recipients were specifically asked which parameter they preferred in their evaluation of oxygenation (PaO_2, SaO_2, or a combination). To ensure the face validity of the questionnaire, we piloted it to six Danish doctors in different hospitals and of various educational levels prior to distribution as recommended,[162] resulting in minimal changes of the questions. The questionnaire was constructed in English without translations to prevent induction of variations in the translational process while maintaining compatibility in all countries as Danish, Norwegian, Swedish, and Finnish doctors are assumed to adequately understand English. The questionnaire was kept short at 17 questions to minimise non-responses or partial questionnaire fulfilment.[163]

3.1.2. Recipient population and distribution

The questionnaire was electronically distributed to a broad sample of Danish, Norwegian, Swedish, Finnish, English, Welsh, and Northern Irish ICU doctors from the April 25 to August 8, 2016. Non-responders and partial responders received

scheduled reminder e-mails 14 and 28 days after the distribution. An additional third reminder e-mail was sent in September 2016.

3.1.3. Statistics

The results were described descriptively and reported as proportions of answers with 95% confidence intervals (95% CI). Supplemental comparisons were conducted using McNemar's test, a p-value < 0.05 was considered statistically significant.

3.2. The observational study (Paper II)

3.2.1. Population

In the preliminary investigation for clarifying current clinical practice, all ABG samples analysed in the specific blood gas analysing apparatuses (ABL800 FLEX®, Radiometer, Copenhagen, Denmark) located in five ICUs in Aalborg University Hospital and North Denmark Regional Hospital, Hjørring in a period from January 1, 2012 to November 27, 2015 was retrieved. The five ICUs were three general ICUs admitting mixed surgical and medical patients, one dedicated cardiothoracic ICU, and one dedicated neuro/trauma-ICU. In the main observational study however, the inclusion period was extended, and the population targeted was specified to include only invasively mechanically ventilated patients in the five ICUs. This was a retrospective study of all invasively mechanically ventilated adults ($\geq$ 15 years of age) admitted throughout a 4.5-year period from January 1, 2012 to June 30, 2016, identified through the administrative ICU database (KoorInt). The study addressed oxygenation levels and levels of FiO_2, specifically including all ABG samples analysed in any ABG apparatus in the two hospitals during invasive mechanical ventilation in the ICU.

3.2.2. Databases and data retrieved

The KoorInt database is an administrative database, which includes all ICU admissions in the North Denmark Region. The registry contains diagnosis-related group (DRG) codes for ICU admissions and discharges including times of these, types of ICU admission (elective surgical, acute surgical or acute medical), codes for various life support, the Simplified Acute Physiology Score II (SAPS II), ICU mortality codes, and certain ICU procedural codes. The codes for ICU admission, invasive mechanical ventilation, and acute dialysis registered in KoorInt have previously been validated as a study investigated the validity of these codes in the Danish National Patient Registry,[164] specifically using a North Denmark Cohort of ICU patients, and the registrations in the Danish National Patient Registry from the North Denmark region are retrieved directly from the KoorInt database. This study established a positive predictive value of the ICU admission code and the invasive mechanical ventilation code of 100% (95% CI: 95.1% to 100%) for the combination

of both codes, and a positive predictive value for the acute dialysis code of 98% (95% CI: 91.0% to 99.0%).[164]

The central server of ABG analyses, Radiance, from which the ABG data was retrieved, contains all analyses conducted in all ABG analysing apparatuses (ABL800 FLEX®, Radiometer, Copenhagen, Denmark) of Aalborg University Hospital and North Denmark Regional Hospital, Hjørring. ABG samples are analysed upon entering or barcoding a valid Civil Personal Register (CPR) number, therefore, all analyses are registered with specific time-points and linkage to the individual patients.

The 90-day mortality from the time of ICU admission were retrieved from the Danish Civil Personal Registration Registry. This registry uses the law-enforced Danish CPR number, unique to all Danish citizens, and contains daily information on the vital status and migration status of all citizens since 1968.[165]

Periods of invasive mechanical ventilation were identified through KoorInt and all ABG data conducted during the periods of invasive mechanical ventilation in any ABG analysing apparatus in the respective hospitals were retrieved from Radiance. In addition, information on gender, age, ICU admission type, use of renal replacement therapy, use of vasopressors and inotropes, SAPS II, and ICU mortality were retrieved from KoorInt. The ICU mortality was cross-checked with the data from the Danish Civil Personal Registration Registry.

3.2.3. Outcomes

The study consisted of a descriptive and an analytical part. In the descriptive part, PaO_2, SaO_2, and FiO_2 levels, proportions ABG samples with hypoxaemia and hyperoxaemia, and FiO_2 adjustments in response to hyperoxaemia were assessed. In the analytical section associations between PaO_2 levels during invasive mechanical ventilation and mortality were assessed in patients admitted to the ICU and in ICU-discharged patients, respectively. The descriptive part included all ABG analyses conducted during invasive mechanical ventilation in all ICU admissions in the 4.5-year period, whereas the analytical part included only the first ICU admission with invasive mechanical ventilation conducted within the 4.5-year period.

3.2.4. Statistics

As all data were non-normally distributed, PaO_2, SaO_2, and FiO_2 levels were reported as medians with interquartile ranges (IQR). Degrees of hypoxaemia and hyperoxaemia were reported as proportions of all ABG samples conducted. Occurrences of uncorrected hyperoxaemia, where the FiO_2 were not reduced in subsequent ABG samples with hyperoxaemia are descriptively reported as proportions of ABGs where FiO_2 could be reduced, defined as $FiO_2 \geq 0.30$ and a

subsequent ABG measurement with a registered FiO_2 level in the same episode of mechanical ventilation.

PaO_2 exposure was estimated using an area-under-the-curve (AUC) PaO_2 measure divided by the exposure time, interpretable as an average PaO_2 level during invasive mechanical ventilation. Associations between exposure-time-divided AUC PaO_2 and mortality were evaluated using a multi-state illness-death model (Figure 1), where hazards of dying (transition intensities) for patients within the ICU (ICU mortality) and for ICU-discharged patients (post-ICU mortality), respectively, were estimated using Cox proportional hazards models adjusting for all covariates: age, gender, admission type, SAPS II, renal replacement therapy within the first 24 hours, vasopressors or inotropes within the first 24 hours, and currently ventilated (yes or no) for patients still within the ICU, and ICU length-of-stay for ICU-discharged patients. The underlying time-scales were time since ICU admission for hazards of dying in the ICU and time since ICU discharge for post-ICU death hazards. We applied multiple imputation to make up for missing admission codes, SAPS II values, and missing times of ABG conductance.

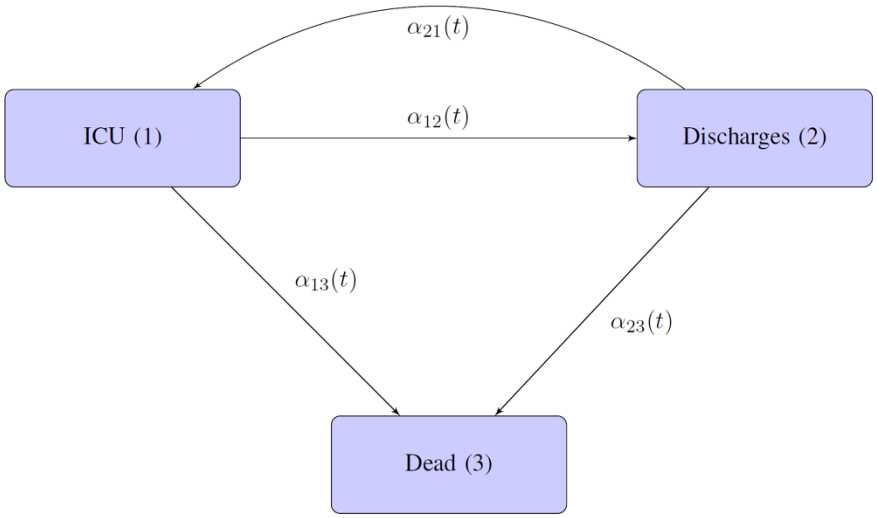

Figure 1 Multi-state illness-death model. ICU: Intensive Care Unit. Depicts the three possible states (1-3) a patient can occupy during the study period and the possible transitions between these states. The α values denote transition intensities (hazards) between states. The α values are time-dependent e.g. $\alpha_{23}(t)$ denotes the intensity of dying on day *t*, giving that the patient is alive and has been discharged from the ICU on day *t*.

3.3. The HOT-ICU trial (Paper III)

Paper III represents the published protocol, outlining the design and rationale for the HOT-ICU trial.

3.3.1. Trial design and setting

The HOT-ICU trial is an investigator-initiated, pragmatic, randomised, outcome-assessment blinded, parallel group trial of two separate PaO_2 targets throughout the duration of ICU admission to a maximum of 90 days. It will include patients in approximately 40 European ICUs in 7 countries, and was initiated with an expected inclusion period of two years.

3.3.2. Eligibility, screening and randomisation

All patients fulfilling the following inclusion criteria within 12 hours from ICU admission will be screened in the system: age 18 years or older, acutely admitted to the ICU, having an indwelling arterial catheter, receiving supplemental oxygen with a flow of at least 10 litres per minute in an open system irrespective of any flow of atmospheric air or an FiO_2 of at least 0.50 in a closed system including invasive or non-invasive ventilation or continuous positive airway pressure (CPAP) systems, and are expected to receive supplemental oxygen for at least 24 hours in the ICU.

We will exclude patients if they cannot be randomised within 12 hours of ICU admission, receive chronic mechanical ventilation for any reason, use home oxygen supplementation, are previously treated with bleomycin, have solid organ transplant planned or conducted during current hospitalisation, are imminently brain dead or withdrawn from active therapy, are pregnant, are carbon monoxide, cyanide or paraquat poisoned, have methaemoglobinaemia, have any condition expected to involve the use of hyperbaric oxygen therapy, have sickle cell disease, or if their consent cannot be obtained according to national regulations, or they have previously been randomised into the HOT-ICU trial.

Randomisation will be conducted electronically via a central web-based screening system with computer-generated allocation sequence lists with permuted block sizes stratified by site and for COPD and active haematological malignancy at baseline

3.3.3. Interventions

Eligible patients will be randomised 1:1 to a PaO_2 target of 8 kPa (intervention group) and a PaO_2 target of 12 kPa (control group) throughout the duration of the ICU admission, including any readmissions, up until 90 days after randomisation. FiO_2 is titrated from 0.21 to 1.00 to obtain the allocated oxygenation target in both intervention groups. Any other treatment supplied in the ICU is at the discretion of

the treating clinicians. The oxygenation targets are not blinded for clinicians, patients, relatives or trial personal (with the exception of outcome assessors and the trial statistician, as stated below).

3.3.4. Trial outcomes

The primary outcome is the 90-day all-cause mortality. Secondary outcomes include days alive without organ support and days alive and out of hospital in the 90-day period; proportion of patients with one or more serious adverse events in the ICU defined as new episode of shock, new ischaemic stroke, or new episode of intestinal or myocardial ischaemia; one-year all-cause mortality; health related quality of life measured using EuroQol 5 dimensions 5 level questionnaire and EuroQol visual analogue scale[166] at one-year follow-up; cognitive and pulmonary function at one-year follow-up in a subgroup; and an overall health economic assessment. Outcome assessment is blinded for the mortality outcomes, the EuroQol outcome, and for the cognitive and pulmonary function test outcomes.

3.3.5. Sample size calculations and statistics

Assuming a mortality of 25% in the control group,[167,168] in order to detect or reject a true 20% relative risk (RR) reduction, with a maximal type 1 error of 5% and type 2 error (power) of 90%, we will include 2,928 patients into the trial. A planned interim analysis will be conducted after 90-day follow-up of the first 1,464 patients equal to 50% of the sample size. The primary outcome will be compared using a generalised linear model with a log-link and binomial error distribution with adjustment for stratification variables. Significance of the intervention will be assessed using p-values and RR with 95% confidence from this regression analysis. A two-sided p-value below 0.05 will be considered statistically significant. A detailed statistical analyses plan will be submitted as a separate publication prior to randomisation of the last patient in the trial, or in the case that the trial is stopped prematurely before inclusion of the planned 2,928 patients, the detailed statistical analyses plan will be submitted prior to the trial database being locked. The trial statistician is blinded for the interventions throughout all analyses.

3.4. Ethics

No ethical permission is required to conduct surveys in the participating countries according to national regulations in Scandinavia and in the United Kingdom (UK). Permission to retrieve non-anonymised data from KoorInt, from ABG samples, and from the Danish Civil Personal Registration Registry without individual patient consent was granted by the Danish Patient Safety Authority (3-3013-1864/1/) as required according to Danish regulations. The HOT-ICU trial was prospectively approved by the Danish Medicines Agency (AAUH-ICU-01), the Committee on Health Research Ethics in the North Denmark Region (N-20170015), and by required

authorities in all participating countries in accordance with national regulations. Informed consent from all included patients, their next-of-kins, as well as any trial guardians in the HOT-ICU trial are obtained in accordance with national regulations. The trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT03174002) and at the European clinical trials database (EudraCT number 2017-000632-34). All studies were approved by the Danish Data Protection Agency (2008-58-0028) and relevant data processing agreements with the Copenhagen Trial Unit were signed for the observational studies, and for the HOT-ICU trial, respectively. An independent data monitoring and safety committee (DMSC) oversees the HOT-ICU trial throughout its duration.

4. Results

4.1. Oxygenation survey (Paper I)

The questionnaire was distributed to 1080 eligible doctors and full or partial responses were received from 681 doctors equal to a response rate of 63%.

4.1.1. Preferred parameter of oxygenation

When asked, which parameter the doctors rated the highest in their evaluation oxygenation in a mechanically ventilated patient in the ICU 52% (95% CI: 48% to 56%) of respondents answered PaO_2, 23% (95% CI: 20% to 27%) answered SaO_2, and 24% (95% CI: 21% to 27%) answered a combination of PaO_2 and SaO_2 (n = 677).

4.1.2. Oxygenation preferences in specified clinical scenarios

The preferences for increasing, decreasing or not changing an FiO_2 of 0.50 in a mechanically ventilated patient revealed that most doctors targeted a PaO_2 of 10 kPa in patients with healthy lungs, ARDS, and abdominal sepsis with 76% (95% CI: 76% to 82%), 73% (95% CI: 70% to 76%), and 76% (95% CI: 73% to 79%) of doctors not changing the FiO_2 at this PaO_2 level, respectively (all p-values < 0.001, McNemar's test for comparisons with proportions of 'no change' answers at PaO_2 level above and below the respective levels); a preference for targeting a PaO_2 of 12 kPa in patients with cerebral or myocardial ischaemia as 67% (95% CI: 64% to 71%) and 67% (95% CI: 63% to 71%) of doctors' would not change the FiO_2 at this PaO_2, respectively (p-values < 0.001 to 0.002), and a preference for targeting 8 kPa in patients with known COPD and habitual hypercapnia as 85% (95% CI: 82% to 87%) would not change the FiO_2 at this PaO_2 level (p-values < 0.001).

4.1.3. Acceptable oxygenation levels in a clinical trial

The highest acceptable oxygenation level in a clinical trial of higher versus lower oxygenation targets was ≥ 12 kPa for 77% (95% CI: 74% to 80%) of the respondents and the lowest acceptable oxygenation target was ≤ 8 kPa for 80% (95% CI: 77% to 83%) of the respondents.

4.2. Observational study (Paper II)

In the preliminary investigation, a total of 261,355 PaO_2 measurements from 7,001 ICU patients were retrieved. The distributions of PaO_2 and SaO_2 values are shown in Table 5.

	ABGs	Mean	SD	Min	2.5%	10%	25%	50%	75%	90%	97.5%	Max
PaO_2 (kPa)	261,355	12.4	4.6	2.2	7.3	8.6	9.7	11.4	13.8	17.1	23.4	87.5
SaO_2 (%)	261,345	96	4	15	88	93	0.95	97	98	99	100	100

Table 5 Distribution of PaO_2 and SaO_2 in ABGs conducted in the five ICUs in the preliminary investigation (unpublished). ABGs: Arterial blood gas samples; SD: standard deviation; Min: range minimum; Max: range maximum, PaO_2: arterial oxygen tension, SaO_2: arterial oxygen saturation; FiO_2: fraction of inspired oxygen. n = 7,001

In the main observational study we included 4,998 patients in the overall cohort, all having ABG analyses conducted while receiving invasive mechanical ventilation in one of the five ICUs, and all admitted within the 4.5-year study period. A total of 177,769 ABG analyses from these patients were included.

4.2.1. Oxygenation levels, proportions of hyperoxaemia, and FiO_2 responses to hyperoxaemia

The median PaO_2 was 11.3 kPa (IQR: 9.8 kPa to 13.6 kPa), median SaO_2 was 97% (IQR: 95% to 99%), and median FiO_2 was 0.40 (IQR: 0.35 to 0.50). A total of 74,028 (41.6%) of the ABG samples had any hyperoxaemia defined as a $PaO_2 \geq 12.0$ kPa, and 21,069 (11.9%) had severe hyperoxaemia defined as a $PaO_2 > 16$ kPa. In more than 50% of the ABG samples with a $PaO_2 \geq 12.0$ kPa and an $FiO_2 < 0.40$, the PaO_2 remained hyperoxaemic, and the FiO_2 had not been reduced, in the following ABG, whereas this was the case for less than 30% of ABG samples with a $PaO_2 \geq 12.0$ kPa and an $FiO_2 \geq 0.50$, and for less than 15% of ABG samples with a $PaO_2 \geq 16.0$ kPa and an $FiO_2 \geq 0.50$.

4.2.2. Mortality associations

Pronounced hyperoxaemia with an exposure-time-divided AUC PaO_2 level > 16 kPa was associated with increased ICU mortality (adjusted HR: 1.66 (95% CI: 1.20 to 2.29)) compared with the normoxaemic reference AUC PaO_2 interval of ≥ 8 kPa to < 12 kPa, and similarly was hypoxaemia with an AUC $PaO_2 < 8.0$ kPa associated with increased ICU mortality (adjusted HR: 6.24 (95% CI: 3.17–12.25)). Moderate hyperoxaemia with AUC $PaO_2 \geq 12$ kPa to ≤ 16 kPa was not associated with increased ICU mortality (adjusted HR: 1.00 (95% CI: 0.82–1.23)). When censoring patients upon the first ABG with a PaO_2 below 8 kPa to minimise contamination from increased mortality due to hypoxaemia, all associations between increased mortality and hyperoxaemia were accentuated.

No associations between any level of hyperoxaemia or hypoxaemia and increased mortality in ICU-discharged patients were found.

4.3. The HOT-ICU trial (Paper III)

4.3.1. Trial status

The HOT-ICU trial was initiated at Aalborg University Hospital on June 20, 2017. The trial is currently ongoing, recruiting patients in Denmark (19 sites), Finland (4 sites), the Netherlands (2 sites), Switzerland (2 sites) and Norway (1 site). An additional 6-7 sites in the UK await trial initiation in summer 2019. Initiation of the

expected 2 trial sites in Iceland has not yet been planned. Currently on April 21, 2019, 1,639 patients of the planned 2,928 patients have been included. The scheduled interim analysis after full 90-day follow-up of 1,464 patients will be conducted after June 2, 2019.

HOT-ICU trial inclusion rate compared to the inclusion rate necessary to complete the trial within the planned two years of recruitment is presented in Figure 2.

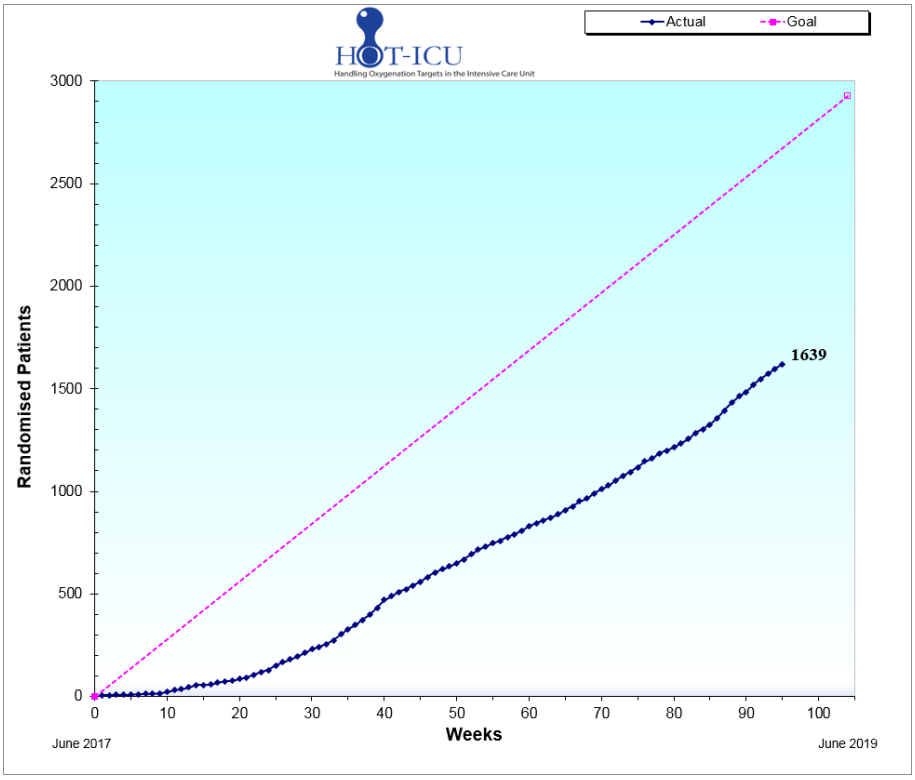

Figure 2 Inclusion rate by weeks in the HOT-ICU trial. Actual inclusion rate versus inclusion rate needed (Goal) to complete the trial within the planned two years of recruitment (status on April 21, 2019)

5. Discussion

5.1. Oxygenation survey (Paper I)

We sought to target a general, broad population of ICU doctors' for the oxygenation survey, preferably, this should be conducted in the geographical area of the HOT-ICU trial as the survey should clarify whether doctors' preferences were compatible with the trial design. We used a broad sample of hospitals, which were included on the base of our local contacts in the respective countries. In all hospitals, except for in the UK, all doctors with any function in the ICU were included ensuring complete representation of all doctors handling patients in the ICU at each site. The surveyed population thus included both consultants, registrars, and trainees. In the UK however, due to the availability for our local contacts, only doctors employed as head of the ICU, and/or the doctors responsible for conducting audits were included, this resulted in more hospitals in the UK included, however with fewer recipients at each hospital.

We used personalised email distribution of the questionnaire, this was chosen since this enabled us to target a large recipient population, and still ensure complete overview of response rates, which would not be possible with the alternative of website self-completion where the precise number of recipients and the relevance of these would not be known. A pre-planned schedule of distribution and reminder-emails was followed with the exception of an extra reminder e-mail send-out to avoid low response-rates due to overlap with summer holiday season, which was indicated by the scheduled distribution and reminder e-mails resulting in many automatic out-of-office e-mail replies.

We chose primarily to describe the survey results descriptively, although supplemental analyses were conducted in questions were it seemed relevant to establish whether observed differences between answers could be considered statistically significant. In most cases, these differences were obvious however, since no overlap of 95% CIs was present, and so, the comparative statistical tests conducted, can largely be considered redundant.

5.1.1. Limitations

The use of a convenience sample of hospitals was not optimal, as this could not necessarily be considered representative of the entire population of ICU doctors, especially not as the number of included hospitals and doctors varied from country to country. Nevertheless, since we wanted to specifically target the departments, which were to participate in the HOT-ICU trial, the included departments in each country to some degree reflects HOT-ICU trial participation, which in this aspect can be considered optimal. The difference between doctors targeted in the UK and in the

Scandinavian countries also represents a limitation. Nevertheless, since we refrained from conducting inter-geographical comparisons of answers, we believe that the overall results are representative for ICU doctors' preferences in the participating countries, and that the differences in target populations can be considered of minor importance.

The lack of SpO_2 as an answer, when evaluating the preferred oxygenation parameter, may have resulted in some respondents specifically preferring PaO_2 to SaO_2 only because the PaO_2 value adds new knowledge to the SpO_2, which the SaO_2 does not. This interpretation however, was not the intent of the question. Nevertheless, since SpO_2 is mandatory in all mechanically ventilated patients for the continuous oxygenation monitoring and FiO_2 titration, it is our opinion that it would have been problematic to have included this parameter in the question along the PaO_2 and the SaO_2. The SpO_2 is a markedly different parameter from the invasive oxygenation measures, and so, the parameters would not have been comparable. Furthermore, if a doctor preferred to target saturation-levels in general, being SpO_2 or SaO_2 levels, the obvious selection of the available parameters would in our opinion have been the SaO_2.

5.1.2. Main findings and implications for the HOT-ICU trial

The preferred parameter for evaluation of oxygenation was PaO_2 for most doctors. In itself, this made the survey results more interesting, since this is the first survey to primarily focus on PaO_2 instead of SaO_2[123,130,136], thus being more in line with the ICU doctors' daily clinical evaluations. Importantly, this also confirmed that the decision to target PaO_2 in the HOT-ICU trial conformed to the prevailing preference amongst ICU doctors in most of the participating countries. Furthermore, the large majority of doctors selected the acceptable highest and the acceptable lowest target in a clinical trial to be at the level of the 8 kPa and the 12 kPa PaO_2 target in the HOT-ICU trial, respectively, or more extreme. We therefore concluded from the survey results that the oxygenation targets of the HOT-ICU trial seemed implementable as both the targeted levels and the specific target parameter were acceptable from the participating doctors' points of view.

5.2. Observational study (Paper II)

In the preliminary unpublished investigation we wanted to conduct a simple clarification of the current clinical practice in the ICUs of the North Denmark Region. Based on the preliminary results therefrom, we decided to target the invasively mechanically ventilated patients more precisely than what was possible on the base of ABG samples alone. The invasively mechanically ventilated subpopulation was selected since when designing the observational study it was the plan that the HOT-ICU trial should include invasively mechanically ventilated patients only. Furthermore, the oxygen supplementation level here is clear-cut with precise FiO_2

available, and since this is likely the ICU subpopulation exposed to the highest levels of oxygen, which in combination with a potential interaction between harm from mechanical ventilation and harm from hyperoxia[86–92] would make associations between mortality and hyperoxaemia most prevalent in this specific subgroup. Such associations seemed interesting as no large observational studies investigating associations between mortality and hyperoxaemia throughout the duration of mechanical ventilation in the ICU had been conducted when the observational study was planned. Recently however, a Dutch study has investigated this in a similar set-up,[9] finding comparable levels of PaO_2 to ours, with median PaO_2 of 10,8 kPa (IQR: 9.3 kPa to 13.0 kPa) in the overall ICU cohort, and establishing associations between hyperoxaemia and increased in-hospital mortality in several different metrics in the mechanically ventilated subpopulation. However, the associations was present only at higher degrees of hyperoxaemia with PaO_2 above 26.7 kPa compared to time-divided AUC PaO_2 above 16 kPa in our study. The Dutch study was an observational study conducted during the implementation of a conservative oxygenation strategy in a two-step before-and-after trial.[152] Therefore, this observational study is essentially a supplementary analysis of an interventional trial. This fact may skew the observational results, because when an overall conservative oxygenation strategy is extensively promoted, any deviation from this strategy by clinicians would require very good arguments. Such an argument could indeed be that a patient was more severely ill in non-respiratory organ systems with an increased mortality risk on the base of this, thus decreasing the chance that the associations observed in the Dutch observational study are actually causal. Nevertheless, our results support their findings.

5.2.1. Limitations

The preliminary investigation had one major limitation, which was that the included patients were exclusively defined from the conducted arterial blood gas samples. This means that ICU patients could have been admitted during the inclusion period, having ABG samples analysed in ABG apparatuses in other departments of the hospital without being included in the study. Furthermore, if ABG samples of non-ICU patients were analysed in the ICU ABG apparatuses, non-ICU patients could be included in the population as well. Therefore, although this preliminary investigation served the aim of quantifying the current clinical practice for the HOT-ICU trial, it was overall highly flawed. Therefore, we decided to conduct a more thorough study handling the problem of patient selection through the use of the KoorInt database. Since the positive predictive value of the ICU admission and conducted invasive mechanical ventilation codes in this database has been shown to be 100%,[164] the included patients in the final submitted observational study have all been admitted to an ICU within the inclusion period and have all received invasive mechanical ventilation here. Furthermore, the specific selection of patients based on their individual CPR number ensured that all ABG analyses conducted during invasive mechanical ventilation in the ICU was included, regardless of where in the hospital

the ABG was analysed. The limitations in the final observational study include the lack of ventilator parameters other than the FiO_2 when evaluating responses to hyperoxaemia. However, as an episode of uncorrected hyperoxaemia required that the FiO_2 was not successively reduces, and that the patient remained hyperoxaemic in the following ABG, any unknown change in ventilator parameters, e.g. a reduction PEEP, would not have had an effect on the hyperoxaemia, and so, the change in ventilator setting can be considered insufficient in correcting the hyperoxaemia. Furthermore, the lack of primary diagnosis codes and knowledge on comorbidities in the mortality analyses is a limitation. The adjustments for the available background information, including admission type, SAPS II score, and use of life support in the first 24 hours however, to some degree make up for this.

5.2.2. Main findings and implications for the HOT-ICU trial

The overall results of the observational study showed that the oxygenation levels of our cohort were markedly more restrictive than what has been observed previously in similar studies,[2,5–7,10–12] and furthermore, the characterisation of adjustments in FiO_2 levels in response to hyperoxaemia similarly showed that uncorrected hyperoxaemia was less prevalent in comparison with previous studies,[3,6,11,128] all indicating that although hyperoxaemia was still frequent, a restrictive oxygenation strategy was prevailing in the included ICUs.

The associations between hyperoxaemia and ICU mortality confirmed the findings in previous studies.[2,9,134,142,169–173] Nevertheless, the association we found seemed to be present at lower degrees of hyperoxaemia than previously identified, which may be due to the restrictive oxygenation strategy in our cohort, or to the analysis of all data throughout the duration of invasive mechanical ventilation, increasing the negative impact of lesser degrees of hyperoxaemia.

We found the overall median oxygenation levels to be very close to the 12 kPa PaO_2 target in the control group of the HOT-ICU trial ratifying that this oxygenation target corresponds to current clinical practice overall. Additionally, the oxygenation levels of the entire ICU population in the preliminary investigation (median PaO_2: 11.4 kPa, IQR: 9.7 kPa to 13.8 kPa) were almost identical to the oxygenation levels found in the main observational study, specifically targeting invasively mechanically ventilated patients (median PaO_2: 11.3 kPa, IQR: 9.8 kPa to 13.6 kPa). Thus, it seems that the oxygenation strategies used in ICU patients of the North Denmark Region did not depend on whether the patients received invasive mechanical ventilation or not. This finding therefore justifies the inclusion of both mechanically ventilated and non-ventilated patients into the HOT-ICU trial with similar oxygenation levels targeted in both groups. The confirmation of an association between hyperoxaemia and increased ICU mortality, which may be present at lower degrees of hyperoxaemia than previously observed, confirms that randomised clinical trials such as the HOT-ICU

trial are highly needed, to clarify whether a causal relationship between excessive oxygen exposure and increased mortality actually exists.

5.3. HOT-ICU trial design (Paper III and Paper IV)

5.3.1. A pragmatic trial

It has been estimated, that only 9% of recommendations in the intensive care clinical guidelines, on which ICU doctors base their daily practice, are supported by solid evidence grade A[174] (Grading of Recommendations, Assessment, Development and Evaluation (GRADE) classification – 'high quality of evidence meaning that we are very confident that the true effect lies close to that of the estimate of the effect'[175]). Therefore, the vast majority of routine interventions used in daily clinical practice in the ICU are conducted without sufficient knowledge on the balance of benefits and harms from the treatment. The only way to evaluate effectiveness of interventions in clinical practice and thus avoid possible infliction of harm, is through pragmatic randomised clinical trials, testing the effectiveness in a setting of daily clinical practice with minimal interference apart from the specific trial interventions tested.[176] Essentially, in the ICU the investigation of ubiquitously daily used simple interventions in large pragmatic randomised clinical trials are eminently needed. Oxygen supplementation is such an intervention, and the HOT-ICU trial is such a pragmatic randomised clinical trial.

The HOT-ICU trial investigates the outcome of the implementation of a lower versus a higher oxygenation target in a pragmatic design. And so, all other interventions apart from the fixed oxygenation targets are at the discretion of the treating clinicians. These interventions are assumed to follow regular practice, intending to supply the best possible treatment to any given patient taking the full condition into account, which includes the fixed higher or lower oxygenation target.[176] This means that ventilator parameters apart from the FiO_2, and instigation of supportive measures of oxygenation like the use of mechanical ventilation, prone positioning, inhaled vasodilators, or ECMO may differ between groups. However, since implementation of any oxygenation target established to be opportune after finishing the trial, would likely include similar changes in ventilator parameters or supportive measures, the effect of differences here can be regarded as a direct consequence of the specific oxygenation targets and should thus be allowed. Therefore, we deliberately refrained from defining acceptable ventilator settings, flow-charts for FiO_2 and PEEP titration, or criteria for implementing supportive measures of oxygenation. Since relevant ventilator parameters and use of supportive measures however, are registered daily in the electronic case report form (eCRF), any between-group differences here are easily reported, allowing these to be taken into consideration when assessing the trial results in the end. Furthermore, the stratified randomisation by site ensures that any differences in ICU treatment conducted of the base of local preferences will to a large extend be equally distributed between the intervention groups.

The choice using point oxygenation targets was pragmatic in nature, since a point target is adaptable to the specific patient (the goal is to be as close to the specified target as possible in any given patient). If a target PaO_2 interval was used, which is the practice in most other trials in the field,[146,148,150–154,158] the variability of PaO_2 in some patients would make them hard to keep within the allocated target interval. This problem does not occur with a point target, since there is no clear-cut definition of how close to the target a patient should be. As long as any deviations overlap the target, an effort to follow the protocol by treating clinicians can be assumed. Furthermore, when addressing the already conducted large trials on the subject using target intervals, the obtained oxygenation levels often center around the least extreme limit of the target intervals, which means that the targets used in these cases effectively seem to equal point targets corresponding to this least extreme interval limit.[146,148,151,152,154] This increases the risk of overlap between the intervention groups, which can be seen in the fact that median oxygenation levels obtained in some cases are above the targeted intervals of the restrictive oxygenation strategies.[146,148,151,152,154] Of course, this deviation may also to some extend be due to the impossibility to decrease below an FiO_2 of 0.21. The choice of targeting a PaO_2 level instead of the more commonly used SaO_2 and SpO_2 parameters,[146,151,154,158] are based on the oxygenation survey results, as well as on several other considerations primarily being a better targeting of normoxaemia and avoidance of hyperoxaemia in the liberal oxygenation group, and an expected better separation of the intervention groups in the end. All relevant arguments for the choice of the targeted PaO_2 oxygenation parameter are presented in the editorial, Paper II (Appendix D).

The pragmatic design also came into play when defining the target population of the HOT-ICU trial. We intended to include all ICU patients with hypoxaemic respiratory failure and hence a certain need for oxygen supplementation, ensuring a difference in oxygen exposure between the intervention groups of a clinically relevant magnitude. Otherwise, we intended to have as broad an inclusion as possible, aware that if not, the results would likely be extrapolated to excluded patient populations afterwards, a practice which seems at best avoided in a pragmatic trial by targeting the entire relevant patient population form a start. Therefore, we did not want to make any assumptions of positive effects of a given oxygenation strategy in any subgroups unless this was supported by solid evidence. And so, the trial includes all ICU patients, were equipoise of the two oxygenation targets can be assumed. This is regardless of whether the PaO_2 target of 8 kPa or the PaO_2 target of 12 kPa in a specific subpopulation would be considered the standard clinical practice. I.e. in patients with COPD[95,96] and in patients with ARDS,[79,80] a PaO_2 target of 8 kPa could likely be considered standard clinical practice. Nevertheless, equipoise of the two oxygenation targets in these subpopulations is present as discussed below, justifying trial inclusion of these even though one could regard the interventional arm and the control arm as being switched. More details on selected specific subpopulations in the HOT-ICU trial and justifications for inclusion of these in separate can be found in the following sections.

5.3.2. Chronic obstructive pulmonary disease

In 2010 a Tasmanian randomised clinical trial of titrated oxygen supplementation to an SpO_2 of 88% to 92% versus standard oxygen supplementation of 8 to 10 L/min through non-rebreather facemask in the prehospital setting, including patients with suspected exacerbations of COPD, found a reduction in the relative mortality risk of 58% in the titrated oxygenation group.[177] As a consequence of this trial, such a titrated oxygenation strategy is recommended for patients with COPD or other chronic conditions with similar risk of hypercapnic acidosis in clinical guidelines of oxygen therapy in acutely ill patients.[95,96,178] Patients in the ICU however, may differ from these recommendations, and are also specifically disclaimed to be included in the overall guidelines on the subject.[95,96] Furthermore, the only randomised clinical trial conducted in patients with COPD exacerbation admitted to the ICU, a pilot trial of 36 patients, did not find any differences between a higher versus a lower oxygenation strategy, neither in clinical outcome nor in pH or $PaCO_2$ levels.[144] The targets used in this trial were lower (PaO_2 > 6.6 kPa versus PaO_2 > 9.0 kPa) than in the prehospital Tasmanian trial,[177] the achieved PaO_2 levels however, were 9-10 kPa in the restrictive oxygenation group versus 12-15 kPa in the liberal group, which are at the level of the achieved PaO_2 levels in the Tasmanian trial. Additionally, the Tasmanian prehospital trial[177] investigated fixed high-flow oxygen supplementation versus a targeted oxygenation strategy. This means that the majority of patients in the liberal oxygenation group of this trial may likely have been hyperoxaemic with PaO_2 levels above the normal physiological range, and so, no conclusions regarding a strictly normoxaemic oxygenation target corresponding to the 12 kPa PaO_2 target in the HOT-ICU trial, can be deducted therefrom. Furthermore, the prehospital setting is markedly different than the ICU setting in regards to levels of monitoring, especially of the $PaCO_2$, and the possibilities to use supportive measures like non-invasive or invasive mechanical ventilation. This could likely counteract harm from hyperoxic hypercapnia or avoid it completely.[109,110] In summary, for hypoxaemic patients with COPD admitted to the ICU, the optimal oxygenation target overall remains unknown, and equipoise of a titrated strictly normoxaemic oxygenation strategy (e.g. a PaO_2 of 12 kPa) and a titrated low normoxaemic oxygenation strategy (e.g. a PaO_2 of 8 kPa) is present. Furthermore, up to 1/3 of COPD patients are undiagnosed,[179] and 27% of non-COPD patients with a history of smoking, who attends primary care with acute respiratory tract infection have an unknown COPD diagnosis.[180] Therefore, even with an exclusion criteria of COPD, numerous patients with undiagnosed COPD would still be included into the HOT-ICU trial. Since the COPD population, primarily due to hyperoxic hypercapnia, may react differently to oxygen supplementation than the rest of the HOT-ICU population, COPD at baseline was included as a stratification variable.

5.3.3. Acute respiratory distress syndrome

An oxygenation strategy targeting a PaO_2 of 7.3 kPa to 10.7 kPa has been a part of the ARDS Network protocol since their large trials conducted in the beginning of the century.[79,80] Nevertheless, these oxygenation targets are not based on solid evidence as no randomised controlled trials on higher versus lower oxygenation levels in patients with ARDS have been conducted. Coherently, no recommendations of specific oxygenation levels are included in clinical guidelines of mechanical ventilation in ARDS.[181,182] The recommendations of restrictive oxygenation targets are generally aimed at minimising pulmonary oxygen exposure to avoid oxidative stress adding to the already existing severe respiratory failure in this patient population, thus protecting the lungs.[16–18,49,53] However, even though the focus on protecting the lungs may seem opportune, the mortality in ARDS are only directly caused by respiratory failure in estimated 16%[183] or 13% to 19%[184] of deaths, whereas death from multi-organ-failure and sepsis are far more prevalent.[183,184] Such multi-organ-failure or sepsis could potentially be aggravated or indeed caused by localised in-evident tissue hypoxia. Therefore, in the effort of protecting the lungs, it may be that we actually increase the risk of dying from complications related to hypoxia, and if so, this may not be obvious in the daily clinical practice. Furthermore, the oxygenation practices used in the ARDS population worldwide are generally far more liberal than the ARDS Network recommendations as a median PaO_2 of 12.4 kPa was recently found in a worldwide observational study of patients with ARDS.[133] And so, although the ARDS Network's target range might be considered the best clinical practice in patients with ARDS, a PaO_2 target around 12 kPa seems to be the current clinical practice. In summary, the optimal oxygenation target in patients with ARDS remains unknown, no firm evidence supports any strategy and clinical practice seems far more liberal, than recommended. Therefore, equipoise of a strictly normoxaemic oxygenation target and a low normoxaemic oxygenation target in the ARDS population is present.

5.3.4. Neuro-intensive care

Several randomised clinical trials on lower versus higher oxygenation levels in in neuro-intensive care patients have been conducted. The populations of these trials include ICU patients with traumatic brain injury,[147,149], ICU patients with acute stroke,[145] and patients with possible anoxic brain injury following resuscitation from cardiac arrest, conducted either prehospitally[185,186] or in the ICU.[150] All of these trials however, are small pilot trials, and the two of them, which actually detect any differences in relevant clinical outcomes seem to be of a very poor quality, not reporting procedures of randomisation and allocation, or reasons for drop-outs.[145,147] In addition, a large randomised clinical trial in 8,003 patients with acute ischaemic stroke outside the ICU[77] did not find beneficial effects of oxygen supplementation in non-hypoxaemic patients with $SpO_2 \geq 90\%$, hereby confirming previous similar results in smaller trials.[187,188] A PaO_2 above 10 kPa has been proposed for patients

with concomitant traumatic brain injury and respiratory failure,[189] however, this target is apparently without solid evidence base. Since no clinical evidence supports the traditional liberal oxygenation strategies in neuro-intensive care, and since evidence from large randomised trials of neurologically injured patients in other settings supports use of low oxygenation targets equal to the low 8 kPa PaO_2 target used in the HOT-ICU trial, equipoise of such a low oxygenation target and a strictly normoxaemic oxygenation PaO_2 target of 12 kPa seems to be present, and hence the HOT-ICU trial includes neuro-intensive care patients of various pathogeneses.

5.3.5. Outcome considerations

The primary outcome of 90-day mortality was selected as only the mortality will weigh the totality of all the possible harms and/or benefits from a higher or a lower oxygenation strategy, respectively. Furthermore, mortality is a patient relevant outcome, and it is a binary hard outcome in nature and is therefore highly objective. Furthermore, we consider oxygen supplementation to be such a vital part of life-support that the estimated RR reduction of 20%, equal to an absolute risk reduction of 5% with an estimated 25% mortality in the control group, is realistic. Especially, as the estimated absolute risk reduction of 5% is lower than generally estimated in conducted ICU trials, which has a tendency of being underpowered.[190] In addition, the control group mortality is estimated from the overall mortality in the acutely admitted ICU population,[167,168] and since the patients included in the HOT-ICU trial because of their hypoxaemic respiratory failure, do not necessarily represent the average, the estimated control group mortality may be on the conservative side. The risk of having overestimated the control group mortality, which is a tendency in ICU trials, specifically in trials including patients with sepsis and septic shock,[191] should therefore be low. Since the patient population with active haematological malignancy has an excessively high ICU mortality,[192] this was included as a stratification variable to ensure equal distribution between groups.

The secondary outcomes include a composite outcome of proportions of patients with one or more new serious adverse events in the ICU, which may be related to the oxygenation target. The included events here are ischaemic events, which are likely influenced by oxygenation levels,[71,74,193] and new episodes of shock, as the liberal oxygenation control group in the largest published randomised controlled trial on higher versus lower oxygenation levels in the ICU had a significantly higher prevalence of shock.[153] The use of a composite end point might be problematic, especially if the composite elements cannot be counted as equally relevant or harmful. This may be considered the case with the ‘new shock’ element, as this element may seem less patient relevant than the ischaemic events. Nevertheless, the mortality of patients having shock is high from 22%[194] to 45%,[195] and is significantly higher than in patients without shock,[194] justifying the inclusion of this element in the composite outcome. If a separate element of the composite outcome turns out to be far more prevalent than the other elements, thus overshadowing these, this may represent a

problem. To ameliorate this however, we will report all the specific elements of the composite outcome in separate as well. We have also included the secondary outcome of days alive without organ support in the 90-day follow-up period. This outcome is essentially an alternative to the predominating ICU length-of-stay outcome.[190] Given the large variability in ICU beds per citizen[19] and in ICU mortality between countries,[20] the outcome of ICU length-of-stay would likely be highly variable, as the disease severity criteria for being in the ICU is highly differentiated.[21] The days alive without organ support outcome however, is less dependent on the different criteria for being admitted to an ICU between countries, and less dependent on individual accrued extra variable admission time,[196] as the use of organ support primarily depends on the patient condition, and therefore will naturally be a more homogenous outcome than the ICU length-of-stay. Finally, the supplemental one-year follow-up outcomes of cognitive and pulmonary function tests are relevant to discuss. The cognitive function test has been included, since hypoxaemia during ICU admission with ARDS has been associated with impaired long-term cognitive function.[143] However, whether this is in fact a causal relationship, or whether hypoxaemia is just a surrogate marker for disease severity during the ICU admission, which causes a higher degree of post-ICU neurological deficit, requires a randomised controlled trial to determine. The HOT-ICU trial represents a unique possibility to clarify this. Similarly, since high FiO_2, and the oxygen toxicity caused by this, primarily is thought to elicit pulmonary damage,[16–18,49,53] it seems relevant to investigate whether a thorough pulmonary function test at long-term follow-up is able to detect any between-group differences, corresponding to a permanent pulmonary damage from higher levels of oxygen supplementation during the ICU admission.

6. Conclusions and perspectives

6.1. Oxygenation survey conclusions (Paper I)

The PaO_2 was the preferred oxygenation parameter for Northern European ICU doctors, their preferred PaO_2 target levels ranged from 8 kPa to 12 kPa in mechanically ventilated patients depending on the specific patient categories and finally, the PaO_2 oxygenation targets of 8 kPa and 12 kPa, as used in the HOT-ICU trial, were regarded as within the acceptable range in a clinical trial by most doctors.

6.2. Observational study conclusions (Paper II)

The observed oxygenation levels in ICUs of the North Denmark Region were generally restrictive and although hyperoxaemia was frequent, episodes of uncorrected hyperoxaemia with unchanged FiO_2 remained scarce, especially at $FiO_2 \geq 0.50$. The overall median PaO_2 was close to the control group target PaO_2 of 12 kPa in the HOT-ICU trial, ratifying this to be equal to current clinical practice. The oxygenation levels did not seem to depend upon whether the patients were mechanically ventilated or not. Finally, an association between increased ICU mortality and severe hyperoxaemia during invasive mechanical ventilation with exposure-time divided AUC $PaO_2 > 16$ kPa was identified. No associations at lower levels of hyperoxaemia or between PaO_2 levels and post-ICU mortality however, were found.

6.3. The HOT-ICU trial conclusions (Paper III)

The HOT-ICU trial is more than half-way through trial inclusion, approaching the planned interim analysis. Patients are actively recruited in five European countries and additionally two countries are preparing initiation. Trial inclusion are expected to be completed within the next year, approximately one year behind planned schedule.

6.4. Perspectives

The conducted studies were pivotal in designing and initiating the HOT-ICU trial. The trial is running, and currently represents the largest randomised clinical trial on lower versus higher levels of oxygenation in patients admitted to the ICU. The primary outcome is the 90-day mortality, however, several highly patient relevant long-term outcomes are investigated as well, including health-related quality of life, and cognitive and pulmonary function. The results of the HOT-ICU trial will likely add substantially to the knowledge on optimal oxygenation targets in the ICU, and will hopefully aid in ensuring a more evidence based approach to oxygen supplementation in the ICU for the benefit of patients and healthcare systems alike.

7. Funding and conflicts of interest

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Appendices

Appendix A. Paper I

Schjørring, OL et al; Intensive care doctors' preferences for arterial oxygen tension levels in mechanically ventilated patients; Acta Anaesthesiol Scand. 2018 Nov;62(10):1443-1451. doi: 10.1111/aas.13171.

Link: https://onlinelibrary.wiley.com/doi/full/10.1111/aas.13171

Appendix B. Paper II

Schjørring, OL et al: Arterial oxygen tensions in mechanically ventilated patients in the intensive care unit: a descriptive study of hyperoxaemia and associations with mortality; Article draft, submitted to Intensive Care Medicine on April 17, 2019

Appendix C. Paper III

Schjørring, OL et al: Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) - Protocol for a randomised clinical trial comparing a lower vs a higher oxygenation target in adults with acute hypoxaemic respiratory failure; Acta Anaesthesiol Scand. 2019 Mar 18. doi: 10.1111/aas.13356. [Epub ahead of print]

Link: https://onlinelibrary.wiley.com/doi/full/10.1111/aas.13356

Appendix D. Paper IV

Schjørring, OL et Rasmussen, BS: The paramount parameter: arterial oxygen tension versus arterial oxygen saturation as target in trials on oxygenation in intensive care; Crit Care. 2018 Nov 22;22(1):324. doi: 10.1186/s13054-018-2257-9.

Link: https://ccforum.biomedcentral.com/articles/10.1186/s13054-018-2257-9

Appendix E. Survey search string

The search string used for identification of current literature on oxygenation surveys in the ICU was:

((((((("Interview"[Publication Type] OR "Interviews as Topic"[Mesh])) OR ("Surveys and Questionnaires"[Mesh])) OR (interview*[tw] OR questionnair*[tw]))) AND ((((("Oxygen Inhalation Therapy"[Mesh]) OR "Oximetry"[Mesh]) OR (Oximetry[tw] OR oxygen inhalation therap*[tw] OR oxygen fraction[tw] OR oxygen saturation[tw])) OR arterial oxygen pressure)) AND ((((((((((("Respiratory Distress Syndrome, Adult"[Mesh]) OR "Acute Lung Injury"[Mesh]) OR (shock lung*[tw] OR acute lung injur*[tw] OR respiratory distress syndrome*[tw])) OR "Respiration, Artificial"[Mesh]) OR mechanical ventilation*[tw]) OR (noninvasive ventilation*[tw] OR non invasive ventilation*[tw] OR noninvasive positive pressure ventilation*[tw] OR non invasive positive pressure ventialtion*[tw])) OR "Continuous Positive Airway Pressure"[Mesh]) OR Continuous Positive Airway Pressure*[tw]) OR (high flow nasal cannula*[tw] OR high flow nasal oxygen[tw])) OR (critical care[tw] OR intensive care[tw])) OR (((((("Intensive Care Units"[Mesh:noexp]) OR "Burn Units"[Mesh]) OR "Coronary Care Units"[Mesh]) OR "Recovery Room"[Mesh]) OR "Respiratory Care Units"[Mesh])) OR "Critical Care"[Mesh:noexp])

The last search in Medical Literature Analysis and Retrieval System Online (MEDLINE) on March 29, 2019 identified 940 hits, from which the reported studies in Table 2 were extracted.

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