Association between Conventional Oxygen Therapy and Characteristics and Outcomes of Adult Patients in a Surgical Intensive Care Unit

Lubov Stroh

Heidelberg University Hospital

Dennis Nurjadi

Heidelberg University Hospital

Florian Uhle

Heidelberg University Hospital

Thomas Bruckner

Heidelberg University Hospital

Markus A. Weigand

Heidelberg University Hospital

Mascha O. Fiedler (✉ Mascha.Fiedler@med.uni-heidelberg.de)

Heidelberg University Hospital

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Abstract

Background: Oxygen therapy is often used in emergency departments and intensive care units. The prevention of hypoxia with associated complications remains the main target, but a high-concentrated usual oxygen therapy seems not to be the best strategy. We hypothesize that physiological pressure of arterial oxygen (paO_2) reduces mortality, onset of new infections and organ dysfunctions in critically ill patients compared with supraphysiological paO_2 .

Methods: In this retrospective exploratory cohort study we included 112 critically ill adult patients treated in a surgical critical care unit. All patients were assigned to two groups defined a priori based on paO_2 mean values measured in the first 24 hours of mechanical ventilation: first group paO_2 75-100 mmHg ($n=43$), second group patients with $\text{paO}_2 > 100\text{mmHg}$ ($n=69$). Primary outcome was the cumulative survival, defined from the day of admission in the intensive care unit (ICU) until death or end of the hospital stay. Secondary outcome was the incidence of infections and new organ dysfunctions in both groups.

Results: The baseline characteristics like age, body mass index (BMI), lactate and severity of disease scores were similar in both groups. A total of 27 of 69 patients (39,1%) in the group $\text{paO}_2 > 100\text{mmHg}$ and 12 of 43 patients (27,9%) in the group paO_2 75-100mmHg died during their ICU stay or further hospital stay ($p=0.54$). There were no statistically significant differences in the incidence of new infections and new organ dysfunctions between the two groups. Positive end expiratory pressure (PEEP) and fraction of inspired oxygen (F_iO_2) were in the group of patients with $\text{paO}_2 > 100\text{mmHg}$ significantly lower 8,4 mbar vs. 9,5 mbar ($p=0.03$).

Conclusions: There was no significant increase in overall mortality or new onset of infections and organ dysfunctions in critically ill adult ICU patients requiring oxygen therapy with supraphysiological paO_2 ($> 100\text{ mmHg}$) compared to patients with physiological paO_2 (75-100 mmHg). Further studies are needed to define the optimal paO_2 parameter.

Background

Oxygen therapy is one of the primary supportive care for patients with or at risk of developing hypoxic respiratory failure admitted to the emergency department and intensive care units. Severe illness and underlying conditions can lead to low oxygen saturation in the blood, posing a risk for low tissue oxygen levels (hypoxia), ultimately leading to organ dysfunction and failure. To prevent or treat hypoxia, critically ill patients are given oxygen via oxygen masks or during mechanical ventilation in intubated patients. Although prolonged liberal oxygen therapy was often performed to protect patients from possible organ damage caused by hypoxia, the opinion regarding oxygen therapy in the last two decades has fundamentally changed^{3,5}. Numerous studies demonstrated that hyperoxia (too much oxygen) can also be harmful and is associated with unfavourable outcomes.

The prevention of hypoxia and its associated complications like hypoxic brain damage further remains the main focus, but a high-concentrated liberal oxygen therapy may not be the best strategy. The minimum value for partial pressure of oxygen before organ functions are jeopardized, thus harmful for the patient, is not clearly defined. Several studies showed that supraphysiological oxygenation with arterial pressure of oxygen (paO_2) of more than 75-100mmHg is associated with negative effects on the central nervous system (headache, dizziness, neuropathy), on the cardiovascular system (lower cardiac output, coronary blood flow¹⁰), and may lead to hyperoxic vasoconstriction¹¹ on pulmonary system with atelectasis. Furthermore, the use of high inspiratory oxygen fraction causes increased oxidative stress due to radical oxygen species (ROS)². The lungs are the most affected organ by oxygen toxicity. In an older study from 1985 lung damage in an intubated mouse was observed after oxygen therapy with 100% oxygen concentration after 24 hours¹⁵. Some studies report increased risk of mortality in critically ill patients associated with hyperoxia⁵⁻⁷.

In the presented retrospective, exploratory, monocentric study we analysed clinical outcome of intubated and mechanically ventilated adults admitted to a surgical intensive care unit. The aim of our study was to investigate supraphysiologic oxygenation, defined as arterial partial pressure of oxygen (paO_2) more than 100 mmHg per 24 hours, increases mortality. Further, the incidence of organ dysfunction or failures and infections was investigated.

Methods

Study design

This retrospective exploratory cohort study was approved by the Medical Ethics Commission of the Medical Faculty of Heidelberg University, Heidelberg, Germany (S-357/2020) and conducted in accordance to ethical standards of the latest version of the Helsinki Declaration (2013)¹⁷.

Participants

All mechanically ventilated adult patients (≥ 18 years) with ≥ 24 hours hospital stay was screened for inclusion into the study. We excluded non-intubated patients, patients with acute respiratory distress syndrome (ARDS, according to Berlin definition¹⁶) and/or extracorporeal membrane oxygenation (ECMO), patients with severe chronic obstructive pulmonary disease (COPD GOLD IV), brain death, neutropenia and pregnant women. To avoid potential bias, re-admissions to ICU within the same hospitalization were excluded.

Overall, we enrolled 112 patients undergoing elective or emergency surgery, liver transplantation and patients with sepsis or septic shock, post-surgical complications, and haemorrhage that required an admission to the ICU. The patients in the cohort were assigned to two groups according to the paO_2 mean values: group 1 with $\text{paO}_2 \leq 100$ mmHg, group 2 with $\text{paO}_2 > 100$ mmHg. We analysed and calculated

mean values of all paO_2 values from the ABGs (arterial blood gases) measured in the first 24 hours of mechanical ventilation for each patient. Depending on respiratory insufficiency or other causes between 9 and 21 ABG- tests were performed in 24 hours for each patient (figure 1).

Variables

In this study we used data of patients from I-SH/ i.s.h.med (hospital electronic patient record, SAP) admitted to the surgical ICU of Heidelberg University Hospital between 1st January and 31st December 2018 (12 months). We searched systematically for all relevant DRGs (German Diagnosis Related Groups) that were recorded throughout the patient's stay in the ICU and that may be influenced by hyperoxia. Further, we compared the values of common ICU scoring systems, reflecting the severity of disease: sequential organ failure assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE) and Simplified Acute Physiology Score - II (SAPS II) at admission and maximal value during the ICU stay. The inspired oxygen fraction (FiO_2), paO_2 from ABGs, positive end-expiratory pressure (PEEP), lactate averages were defined as the mean value of all measurements within the first 24 hours after admission. Moreover, patients' data included age, body mass index (BMI) and length of stay (LOS) in the ICU. No patient received nitrous oxide.

Primary endpoint of this study was the cumulative survival, defined from the day of admission in the ICU till death or end of the hospital stay. Secondary outcomes were the incidence of infections and new organ dysfunctions in both groups.

Statistical methods

A comprehensive descriptive statistical analysis was conducted with mean, standard deviation, minimum, median, maximum of all continuous data and scores at admission and maximal during the stay. Binary data we reported with absolute and relative frequencies. Baseline demographics, prognostic variables, scores and ventilation modalities were compared between the groups using chi-square and Wilcoxon tests, as appropriate. Cumulative probabilities of survival were plotted using the Kaplan-Meier method and compared using log-rank test. Statistical significance was indicated by p-value (Pearson Chi-Square test and two-sided Wilcoxon Test) below 0.05 for baseline characteristics of patients and the secondary outcomes. SPSS-Software (IBM ® SPSS ® Statistics Version 23) and Microsoft Excel were used for the statistical data analysis.

Results

We enrolled adult patients treated on the surgical ICU of Heidelberg University Hospital from January 2018 to December 2018. 189 patients were identified as potential study participants. A total of 112 met our inclusion criteria and were eligible for the analysis (figure 1). All patients were assigned to two groups: the first group consists of patients with paO_2 75-100 mmHg (n=43), and the second group

patients with $\text{paO}_2 > 100\text{mmHg}$ ($n=69$). The maximum value for paO_2 was 168 mmHg in two patients of group 2.

Cumulative survival

A total of 27 of 69 patients (39, 1%) in the group $\text{paO}_2 > 100\text{mmHg}$ and 12 of 43 patients (27, 9%) in the group paO_2 75-100mmHg died during their ICU stay or further hospital stay. Higher paO_2 was not associated with increased overall mortality. In the Kaplan-Meier survival analysis provided in figure 2 no statistically significant differences between groups were observed in survival estimates ($p= 0.5428$).

Secondary outcomes

There were no statistically significant between-group differences for the incidence of new infections and new organ dysfunctions (DRG Codes) occurred during the ICU stay as shown in table 1. In patients with hemorrhage ($p=0.53$) and polytrauma ($p=0.15$) as a cause for the admission to the ICU more patients received oxygen therapy resulting in $\text{paO}_2 > 100$ mmHg.

Both study groups had similar age, BMI, lactate, and severity of disease scores at admission and during their ICU stay, shown in baseline characteristics in table 2. Of note, PEEP and FiO_2 were in the group of patients with $\text{paO}_2 > 100\text{mmHg}$ significantly lower ($p=0.03$ and $p=0.01$). The patient's group with $\text{paO}_2 > 100\text{mmHg}$ spent an average 1.1 day longer in the ICU ($p=0.59$).

Table 1

DRG – Codes and causes of admission to ICU.

	paO ₂ ≤ 100mmHg, n=43	paO ₂ >100mmHg, n=69	Total (n)	p- value *
DRG-Code				
Atelectasis, n (%)	10 (23%)	15 (22%)	25	1.0000
Pleural effusion, n (%)	30 (70%)	40 (58%)	70	0.2341
Bacterial pneumonia, n (%)	18 (42%)	34 (49%)	52	0.5593
Aspergillosis, n (%)	2 (5%)	8 (12%)	10	0.3122
Acute respiratory failure with hypoxia, n (%)	36 (84%)	56 (81%)	92	0.8041
Sepsis/Septic shock, n (%)	14 (33%)	30 (43%)	44	0.3206
Pneumonia due to sepsis, n (%)	5 (12%)	13 (29%)	18	0.4295
Pyothorax, n (%)	3 (7%)	5 (7%)	8	1.0000
Aspiration pneumonitis, n (%)	2 (5%)	7 (10%)	9	0.4783
Non-healing surgical wound, n (%)	5 (12%)	2 (3%)	7	0.3010
Anastomotic insufficiency, n (%)	2 (5%)	4 (6%)	6	1.0000
Herpes simplex virus pneumonia, n (%)	3 (7%)	5 (7%)	8	1.0000
Acute kidney failure, n (%)	14 (33%)	22 (32%)	36	1.0000
Acute liver failure, n (%)	2 (5%)	9 (13%)	11	0.1992
Delirium, n (%)	13 (30%)	20 (29%)	33	1.0000
Prolonged weaning, n (%)	12 (28%)	13 (19%)	25	0.3509
STEMI/NSTEMI, n (%)	1 (2%)	4 (6%)	5	0.6473
Arrhythmia, n (%)	4 (9%)	12 (17%)	16	0.2784
CIP/CIM, n (%)	3 (7%)	2 (3%)	5	0.3702
MODS, n (%)	5 (12%)	4 (6%)	9	0.3010
Cause of admission to ICU				
Emergency procedure, n (%)	20 (47%)	29 (42%)	49	0.6975
Elective surgery, n (%)	5 (12%)	2 (3%)	7	0.1046
Polytrauma, n (%)	1 (2%)	7 (10%)	8	0.1502
Liver transplant, n (%)	1(2%)	4(6%)	5	0.6473
Complications after surgery, n (%)	15(35%)	29(42%)	44	0.5515

Hemorrhage, n (%)	12(28%)	24(35%)	36	0.5346
Sepsis at admission, n (%)	13(30%)	20(29%)	33	1.0000

ICU= intensive care unit. DRG = German Diagnosis Related Groups. paO2= partial pressure of oxygen. STEMI/ NSTEMI = ST- segment elevation myocardial infarction/ Non-ST segment elevation myocardial infarction. CIP/CIM=Critical-Illness Polyneuropathy/ Critical- Illness Myopathy. MODS= Multi Organ Dysfunction Syndrome. * Pearson Chi-Square test, Pr >= ChiSq (Exact).

Table 2

Baseline characteristics and clinical parameters of study patients.

Variable	paO ₂ ≤ 100mmHg, n=43			paO ₂ > 100mmHg, n=69			P-value, Wilcoxon Test (Two-sided)
	Mean (SD)	Median	Range (min-max)	Mean (SD)	Median	Range (min-max)	
Age	68.1(12.2)	67	31-89	62.8(13.6)	66	23-83	0.09085
BMI	29.5(7.0)	27	20-54	27.5(6.9)	27	17-55.6	0.15102
FiO ₂	45.9(10.3)	46	30-78	40.6(10.4)	38	28-82	0.00292
PaO ₂	93.3(5.7)	96	79-100	118.3(16.4)	113	101-168	-
AdmSAPSII	64.9(20.3)	69	17-106	65.4(19.1)	71	19-94	0.60567
MaxSAPSII	76.4(15.0)	75	45-110	78.3(14.3)	79.5	38-105	0.22591
SOFA	10.6(3.7)	10	4-18	10.8(3.3)	11	2-17	0.56322
MaxSOFA	12.3(3.2)	12	6-19	12.7(2.9)	13	5-18	0.38261
APACHE	29.4(7.9)	29	8-48	30.0(6.7)	31	12-43	0.61746
MaxAPACHE	34.3(6.6)	35	22-48	35.1(5.3)	36	12-44	0.50221
Lactate	28.3(31.8)	14.4	7.7-171.6	21.6(17.6)	14.9	6.8-93.4	0.53771
PEEP	9.5(2.5)	9	5-16	8.4(2.4)	8	5-14	0.02737
LOS	7.9(10.1)	4	1-54	9.1(12.3)	5	1-60	0.59737

SOFA = Sequential organ failure assessment. APACHE= Acute Physiology and Chronic Health Evaluation. SAPS-II = Simplified Acute Physiology Score -II. BMI= Body mass index. PEEP= Positive end expiratory pressure. LOS = Length of stay. FiO₂ = Fraction of inspired oxygen. PaO₂= Partial pressure of oxygen. Positive end expiratory pressure. LOS = Length of stay. FiO₂= Fraction of inspired oxygen. PaO₂= Partial pressure of oxygen.

Discussion

In this retrospective exploratory cohort study, we compared patients with physiological partial pressure of oxygen (paO₂ 75–100 mmHg) and patients with supraphysiological oxygenation with paO₂ over 100mmHg. Interestingly, the highest value in the second group was 168 mmHg in two patients, which is comparably lower than paO₂ values in previous studies, in which hyperoxia was defined as paO₂ of 300 mmHg or greater and was associated either with higher mortality⁹ or with worse neurological outcome¹². This means that in our patient cohort, no excessive oxygenation occurred. Our results are consistent with

the current systematic review with meta-analysis and trial sequential analysis that found neither beneficial nor harmful effects of higher versus lower oxygenation strategies. Similarly, the investigators found no evidence that higher oxygenation versus lower oxygenation had a profound effect on the all-cause mortality¹.

To date, there is no consensus or definitions for cut-off values, as well as the lower and upper limit for partial pressure of oxygen, which differentiate beneficial and harmful effects for the patient. In our patient cohort with relatively small differences in paO_2 values (79–168 mmHg), it was not possible to define this cut-off for paO_2 . Our results differ from those in a previous single-center randomized clinical trial (RCT) by Girardis et al.⁵ In that trial, lower mortality was observed in patients receiving conservative oxygen therapy compared to patients with usual oxygen therapy. The results of this trial could be influenced by initial baseline imbalances between the study groups, such as age, severity of illness, and organ failures. Further, the study was stopped prematurely after increased mortality in one of the study groups in the interim analysis was observed, which may have resulted in an effect overestimation⁴.

Patients with haemorrhage and polytrauma as admission cause were over-represented in the $\text{paO}_2 > 100$ mmHg group (28% vs 35% $p = 0.53$ and 2% vs 10% $p = 0.15$, respectively). These patients often receive oxygen therapy, since clinicians tend to perform oxygen therapy more aggressively in such critical, dynamical situations with potential increased hypoxia risk aggravated by blood loss. Thus, providing a potential explanation for this discrepancy.

Our evaluation certainly presents some limitations. First, this is a single-center study and the patient cohort with 112 enrolled patients is relatively small. In order to define a cut-off for partial pressure of oxygen and to provide more precise and robust estimates of treatment effects, more patients need to be enrolled to achieve an adequate power of analysis. However, the two study groups were well-balanced regarding the baseline characteristics and a detailed analysis was performed in respect to the interaction between all in the intensive care medicine relevant DRG-Codes like sepsis, septic shock, organ transplantation, delirium, prolonged weaning etc. Second, in our study, we investigated the mortality during the hospital stay without follow-up like in other studies, so that mortality in both groups may be underestimated^{13,8}.

Nevertheless, our data implied that paO_2 levels of up to 168 mmHg were not associated with a worse clinical outcome and that supraphysiological paO_2 levels can be tolerated without significant negative effects on the patients, which warrants further scrutiny.

Conclusions

In this study we did not observe any significant differences in mortality nor in new onset of infections and organ dysfunctions between both groups. These results suggest that paO_2 levels between 70 and 170 mmHg could be a reference point in the management of oxygen therapy to avoid excessive supraphysiological potentially toxic paO_2 values and dangerous hypoxia at the same time. Further

studies with larger sample size are needed to clarify the risk-benefit ratio of pursuing a more conservative oxygen treatment strategy in critically ill patients.

Abbreviations

PaO₂ partial pressure of oxygen

F_iO₂ fraction of inspired oxygen

PEEP Positive End Expiratory Pressure

ABG Arterial Blood Gas test

SOFA Sequential Organ Failure Assessment

APACHE Acute Physiology and Chronic Health Evaluation

SAPS-II Simplified Acute Physiology Score II

ARDS Acute Respiratory Distress Syndrome

ECMO Extracorporeal Membrane Oxygenation

COPD Chronic Obstructive Pulmonary Disease

LOS Length of Stay

ICU Intensive Care Unit

BMI Body Mass Index

DRG German Diagnosis Related Groups

STEMI ST-segment Elevation Myocardial Infarction

NSTEMI Non-ST- segment Elevation Myocardial Infarction

Declarations

Ethics approval and consent to participate

This retrospective exploratory cohort study was approved by Medical Ethics Commission of the Medical Faculty of Heidelberg University, Heidelberg, Germany (Votum S-357/2020) and conducted in accordance with ethical standards of the latest version of the Helsinki Declaration (2013)¹⁷.

Consent for publication

Requirement for written informed consent and consent for publication was waived by the Ethics Commission.

Availability of data and materials

All data are stored for at least 10 years. The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

LS helped design the work, analysed and interpreted the data, was a major contributor in writing the manuscript, and critically reviewed and revised the final manuscript. DN and FU helped design the work and critically reviewed and revised the final manuscript. TB helped design the work, analysed the data, critically reviewed and revised the final manuscript. MW helped design the work, critically reviewed and revised the final manuscript. MOF helped design the work, analysed and interpreted the data, drafted the manuscript, and critically reviewed and revised the final manuscript.

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Figures

Figure 1

Patients enrolment in this analysis. ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; paO_2 = arterial partial pressure of oxygen. NIV = non-invasive ventilation.

Figure 2

Kaplan- Meier analysis of cumulative survival from group 1 paO2 75-100 mmHg compared with patients from group 2 paO2 >100mmHg