Incidence of hyperoxia and related in-hospital mortality in critically ill patients: a retrospective data analysis

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Background: Mechanical ventilation with oxygen is life-saving, however, may result in hyperoxia. The aim was to analyse the incidence and duration of hyperoxia burden and related in-hospital mortality in critically ill patients.

Methods: Patients of all ages admitted to intensive care units (ICUs) and with mechanical ventilation for at least seven consecutive days were included in this single centre retrospective medical record audit. The main outcome measure was time-weighted arterial partial pressure of oxygen (PaO_2) over 7 days. Logistic regression for association with in-hospital mortality and propensity score matching was performed.

Results: In total, 20,889 arterial blood gases of 419 patients were analysed. Time-weighted mean PaO_2 was 14.0 ± 2.4 kPa. Time-weighted mean FiO_2 was 49.2 ± 12.1%. Seventy-six (18.1%) patients showed continuous hyperoxia exposure, defined as time-weighted mean PaO_2 > 16 kPa. Duration of hyperoxia, hypoxia (PaO_2 < 8 kPa) and normoxia (PaO_2 8–16 kPa) were 37.9 ± 31.0 h (23.7%), 4.9 ± 9.5 h (3.1%), and 116.8 ± 29.6 h (73.2%). Hyperoxia occurred especially at low to moderate FiO_2 in patients of first and second age quartiles (1–57 years) with smaller SAPS2 score. In-hospital mortality of patients with hyperoxia (32.9%) or normoxia did not differ (35.9%; $P = 0.691$). Conditional logistic regression showed no association between hyperoxia and in-hospital mortality (OR 1.46; 95%CI 0.72–2.96; $P = 0.29$).

Conclusion: Substantial hyperoxia burden was observed in ICU patients. Young patients with less comorbidities showed hyperoxic episodes more often, especially with lower FiO_2. Hyperoxia during 7 days of mechanical ventilation did not correlate to increased in-hospital mortality.

Editorial comment
Exposure to high inspired oxygen levels over many days is thought to be potentially injurious. In this retrospective analysis, at least one week's high inspired oxygen in critically ill ventilated patients did not show increased risk for in-hospital mortality or length of stay, compared to a matched cohort with no hyperoxia exposure.

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In the intensive care unit (ICU), supplemental oxygen (O_2) during invasive mechanical ventilation (IMV) is routinely administered in patients with acute respiratory failure to prevent from organ hypoxia. Beyond doubt, severe hypoxia can contribute to increased ICU morbidity and mortality. Therefore, it has been suggested for years that critically ill patients would benefit from a more liberal O_2 therapy, taking into account that episodes of accidental hyperoxia may also harm the lungs and remote organs.

Recently, it has been proposed that accidental hyperoxia may play a key role in determining patient clinical outcome. Reactive O_2 species, mainly derived from mitochondrial oxidative metabolism with its cytochrome oxidase system, cause inflammatory as well as cytotoxic processes during hyperoxic episodes.[1–3] A retrospective study by De Jonge et al. from 2008 demonstrated a U-shaped association between arterial partial pressure of oxygen (PaO_2) and in-hospital mortality,[4] suggesting that both severe hypoxia and hyperoxia on the first day of ICU admission, may worsen clinical outcome. However, Eastwood et al. could not confirm these findings in a large retrospective data analysis published in 2012.[5] Several smaller retrospective studies in specific ICU subsets, including patients admitted for stroke, traumatic brain injury, and cardiac arrest also found a correlation between hyperoxia and increased in-hospital mortality. Two recent meta-analyses by Damiani et al. in 2014 and Helmerhorst et al. in 2015 conclude that hyperoxia may be associated with poor in-hospital outcome, however, suggest that more clinical evidence is required to better tailor for optimal individual O_2 targets.[6,7]

Oxygen must be regarded as any other drug with potential dose- and time-depended side effects. It is not clearly understood, whether longer exposure (e.g., several days after ICU admission) with significantly elevated oxygen levels result in higher morbidity and mortality. Clinical evidence on the impact of prolonged hyperoxia in ICU patients is lacking, as actual studies only focus on short observation periods (e.g., the first day of ICU admission).

Therefore, the aim of this study was to retrospectively analyse the incidence and duration of hyperoxia burden in ICU patients. A mixed surgical and anaesthesiological cohort of ICU patients undergoing IMV for at least 7 days was investigated to estimate hyperoxic burden during long-term IMV. Hyperoxic burden was correlated with in-hospital mortality to determine if prolonged hyperoxia exposure may be associated with poor clinical outcome in ICU patients.

Methods

Study design and patient inclusion

This single centre retrospective medical record audit was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Vienna, Austria (No. 1428/2014, approved by Prof. Ernst Singer on 15.07.2014). The study data consist of retrospective data subsets collected from seven surgical and anaesthesiological ICUs of the Medical University of Vienna, Austria, collected from January 1st 2009 until April 22nd 2013 with 12909 (3040 $\pm$ 250 annually) admitted patients of which 6735 (1579 $\pm$ 89 annually) received IMV. All patients submitted to one of the ICUs, either planned or unplanned as well as medical or surgical, undergoing positive pressure IMV for at least seven consecutive days after ICU admission were included in the study. The primary outcome variable was time-weighted PaO_2 during 7 days of IMV. Due to the retrospective character of the study, no informed consent of patients or relatives was obtained and the study was not registered in a clinical trials database. Patient data sets with missing values were excluded from the analysis. As all suitable data sets were included, no sample size calculation was performed.

Measurements

The following variables were extracted from the sampling data set for each patient: continuously digitally recorded peripheral hemoglobin O_2 saturation (SaO_2, %) measured by pulse oximetry, and fraction of inspired O_2 (FiO_2, %) assessed from respirator settings; PaO_2 (kPa) and hemoglobin (g/dl) measured by repetitive daily arterial blood gas analyses (ABG) as prescribed by the attending physician. Also, number of ABG samples during the observation period of seven consecutive days after ICU admission, and duration between each recorded

ABG value in the study period were collected from the patient medical records. The issue of consecutive or missing data values was handled as follows. It was assumed that recorded ABG values remained stable over time until a new physiological value was recorded.

Demographics and outcome parameters

Demographic data, the Simplified Acute Physiology Score 2 (SAPS2) on ICU admission, Hospital length of stay (HLOS), ICU length of stay (ICU-LOS), ICU mortality and in-hospital mortality were obtained from the patient medical records.

Calculated values and grouping

Time-weighted mean values of PaO_2 (PaO_2.wmean, kPa) and FiO_2 (FiO_2.wmean, %) were calculated by multiplying the measured individual value with the duration until the next value was obtained divided by the complete time of observation and then taking the sum of all values per patient. The duration of hyperoxic (PaO_2 > 16 kPa, h), normoxic (PaO_2 8–16 kPa, h) and hypoxic (PaO_2 < 8 kPa, h) episodes were identified. In addition, duration of FiO_2 > 50% was calculated and defined as high FiO_2. Also, the maximal PaO_2 value (PaO_2.max, kPa) that occurred during the 7 days of observation was determined for each patient. Patients experiencing continuous hyperoxia (PaO_2.wmean > 16 kPa, PaO_2.H) and patients experiencing normoxia (PaO_2.wmean of 8–16 kPa, PaO_2.N) during all 7 days of observation were identified to test for statistical differences between groups.

All physiological and demographic patient data was gathered from the routine ICU documentation software (CareVue Version 12, Phillips Medical Systems, Andover, MA, USA 2001). Microsoft® Access Version 2013 (Microsoft® Inc., Redmond, Washington) was used to create an anonymized patient database of all collected physiological and demographic patient data.

Statistical analysis

For continuous variables mean and SD and for categorical variables absolute and relative frequencies were calculated. Student's *t*-test was used for continuous variables and Fisher's exact test was used for categorical variables to analyse differences in distributions of covariates.

A propensity score matching was applied to create a balanced subsample of patients. The treatment variable was hyperoxia (i.e., PaO_2.wmean > 16 kPa). For each patient, the probability of being assigned to the hyperoxia group (=propensity score) was calculated from a logistic regression model, where hyperoxia was modeled as a function of the following covariates: age, sex, HLOS, FiO_2.wmean, PaO_2.max, SAPS2, duration of PaO_2 < 8 kPa, duration of FiO_2 > 50% and admission diagnose. Matching was done in a 1 : 1 ratio using the nearest neighbor method as implemented in the R-package "MatchIt".[8]

Using the matched dataset, a conditional logistic regression for matched pairs was calculated to analyse the effect of hyperoxia (PaO_2.H), PaO_2.wmean and PaO_2.max on in-hospital mortality. In addition, a logistic regression model using all patients with in-hospital mortality as dependent variable and PaO_2.H and the propensity score as independent covariates was created. Time-weighted mean PaO_2 values were adapted as predictor variable for the logistic regression by only using the results of day two to seven for calculation, because PaO_2 is also included in the SAPS2. Thereby an overrepresentation of PaO_2 in the model was avoided. The significance level for all tests was 5%. Calculations were performed using the software program R 3.2.0 (www.r-project.com, Vienna, Austria).

Results

Descriptive statistics

The analysis was based on 419 of 554 patients (75.6%) with complete data sets over seven consecutive days. Twenty-nine patients (5.2%) were excluded from the analysis due to missing values for the calculation of SAPS2 score and 106 patients (19.1%) were lacking daily ABG results during the observation period (Fig. 1). The collective consisted of 161 female (38.4%) and 258 male (61.6%) patients with a SAPS2 of 46 ± 18.6. Mean age was 57.8 ± 19.9 years and ranged from 1 to 91 years. Nineteen patients

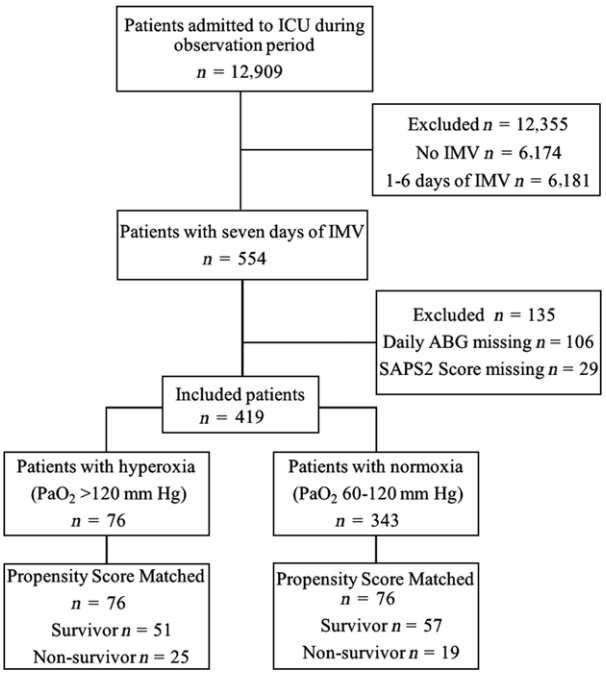

Fig. 1. Flowchart of patients before and after propensity score matching. Abbreviations: IMV, invasive mechanical ventilation; PaO_2, arterial partial pressure of oxygen; SAPS2, simplified acute physiology score 2; ABG, arterial blood gas.

(4.5%) were adolescent during observation with five patients being younger than 6 years (1.2%). The PaO_2.wmean and in-hospital mortality of the excluded patients did not differ significantly from the final study sample. The median ICU stay was 22 days (range 7–189) with an ICU mortality of 30.1% (n = 126). Overall in-hospital mortality in the study sample was 35.3% (n = 148). Additional descriptive patient data is displayed in Table 1.

Hyperoxia, hypoxia and normoxia

In total, 20889 ABG values (in average 49.9 ± 12 ABGs per patient) were analysed. Unweighted mean PaO_2 was 14.5 ± 6.7 kPa and PaO_2.wmean was 14.0 ± 2.4 kPa in all patients over the whole time of observation. Intraday variability in PaO_2.wmean was highest on the first day of IMV on ICU (Fig. 2). PaO_2.max was 34.4 ± 15.3 kPa. A total number of 76 patients (18.1%) showed hyperoxic PaO_2.wmean values (PaO_2.H) and 343 patients (81.9%) showed PaO_2.wmean values between 8–16 kPa, defined as normoxic (PaO_2.N). A PaO_2.wmean < 8 kPa was not observed in any patient. Calculated duration of hyperoxia, normoxia and hypoxia in the study period was 37.9 ± 31.0 h (23.7%), 116.8 ± 29.6 h (73.2%), and 4.9 ± 9.5 h (3.1%), respectively, as shown in Fig. 3. Patients received an unweighted mean FiO_2 of 52.8 ± 15% and FiO_2.wmean of 49.2 ± 12.4% during the study period.

Group differences between PaO_2.H and PaO_2.N are displayed in Table 2. There was no difference between PaO_2.H and PaO_2.N in terms of in-hospital mortality (P = 0.691), ICU-mortality (P = 0.491) or SAPS2 (P = 0.073). Significant differences between PaO_2.H and PaO_2.N were observed for HLOS (P = 0.0003), ICU-LOS (P = 0.039), PaO_2.max (P < 0.0001), and age with the patients of the PaO_2.H group being much younger (43.3 ± 21.6 years vs. 57.3 ± 18.6 years; P < 0.0001, Fig. 4). Also, the PaO_2.H group was less hypoxic (1.7 ± 3.1 h vs. 5.6 ± 10.2 h; P < 0.0001), even though, overall receiving lower levels of FiO_2 (FiO_2.wmean 42.8 ± 9.9% vs. 50.7 ± 12.1%; P < 0.0001, and high FiO_2 30.9 h vs. 63.2 h; P < 0.0001).

Group differences based on mortality

Patients, who deceased during hospital stay were significantly older (P < 0.0001), had higher SAPS2 (P < 0.0001), shorter HLOS (P < 0.0001), a higher FiO_2.wmean (52.5 ± 14.2% vs. 47.5 ± 10.4%; P = 0.0002) and longer duration of high FiO_2 (P = 0.0005). The duration of hypoxia was doubled in these patients (6.8 ± 11.8 h vs. 3.8 ± 7.6 h; P = 0.005). No difference in PaO_2.wmean, PaO_2.max, or duration of hyperoxia was observed compared to patients discharged alive (Table S1).

Propensity score matching

Due to the inhomogeneity in the study sample, to every patient of the PaO_2.H group one patient of the PaO_2.N group with similar propensity score was matched to compensate baseline differences. The final matched collective consisted of 76 pairs of patients while 267 normoxic patients were not used for further analyses. The median ICU stay of the matched pairs was 19 days (range 7–118) with an ICU mortality of

Table 1 Descriptive baseline characteristics of all patients and comparison of matched and unmatched patients.

	Unmatched patients (n = 267)	Matched patients (n = 152)	P value	All patients (n = 419)
Age, years	60.5 (16.22)	44.78 (21.8)	**<0.0001**	57.8 (19.9)
Female, n	93 (34.8%)	68 (44.7%)	**0.048**	161 (38.4%)
SAPS2	46.7 (18.9)	43.0 (17.5)	**0.002**	46.6 (18.6)
PaO_2.wmean, kPa	12.9 (1.6)	16.0 (2.3)	**<0.0001**	14.0 (2.4)
PaO_2.H, n	0	76 (50%)		76 (18.1%)
PaO_2.max, kPa	27.1 (9.7)	47.1 (15.0)	**<0.0001**	34.4 (15.3)
FiO_2.wmean, %	52.5 (12.5)	43.5 (8.9)	**<0.0001**	49.2 (12.1)
Mean SaO_2, %	97.4 (1.6)	98.4 (1.5)	**<0.0001**	97.8 (1.6)
ABG, n per patient	48.5 (11.0)	52.2 (13.3)	**0.003**	49.9 (12.0)
Hemoglobin, g/dl	9.9 (1.2)	10.0 (1.1)	0.593	9.9 (1.2)
Admission diagnose, n				
Cardiovascular	54 (20.2%)	26 (17.1%)	0.628	80 (19.1%)
Respiratory	62 (23.2%)	46 (30.3%)	0.288	108 (25.8%)
Gastrointestinal	52 (19.5%)	17 (11.2%)	0.145	69 (16.5%)
Neurological	49 (18.4%)	36 (23.7%)	0.417	85 (20.3%)
Other	50 (18.7%)	27 (17.8%)	0.903	77 (18.4%)
Duration of (h)				
Hyperoxia	24.7 (19.5)	60.9 (33.9)	**<0.0001**	37.9 (31.0)
Hypoxia	6.7 (11.3)	1.6 (2.8)	**<0.0001**	4.9 (9.5)
HighFiO_2	67.8 (53.5)	39.0 (42.3)	**<0.0001**	57.3 (51.6)
In-hospital mortality, n	104 (39.0%)	44 (28.9%)	**0.040**	148 (35.3%)
ICU mortality, n	89 (33.3%)	37 (24.3%)	0.060	126 (30.1%)
HLOS, d	61.9 (49.9)	45.8 (31.8)	**<0.0001**	56.1 (44.8)
ICU-LOS, d	32.5 (26.8)	24.5 (16.7)	**0.0002**	29.6 (23.9)

Values are mean (SD) and number (proportion). Hyperoxia was defined as PaO_2 > 16 kPa, hypoxia as PaO_2 < 8 kPa, respectively. High FiO_2 was defined as duration in hours (SD) with FiO_2 > 50%. Bold values indicate statistical significance. ABG, arterial blood gas analysis; FiO_2, fraction of inspired oxygen; h, hour; HLOS, hospital length of stay; ICU, intensive care unit; ICU-LOS, intensive care unit length of stay; SaO_2, arterial hemoglobin oxygen saturation; SAPS2, simplified acute physiology score 2; PaO_2, arterial partial pressure of oxygen.

24.3% (n = 37). Overall in-hospital mortality in the matched study sample was 28.9% (n = 44). After propensity score matching, the two groups did not differ statistically significant in demographic and respiratory data except for PaO_2wmean (14.2 ± 1.1 kPa vs. 17.7 ± 1.7 kPa; P < 0.0001). Patients in the PaO_2.H group had higher in-hospital mortality (32.9% vs. 25.0%; P = 0.28) and ICU mortality (26.3% vs. 22.4%; P = 0.57) as compared to matched patients of the PaO_2.N group, without being statistically significant.

Logistic regression

Univariate unadjusted logistic regression showed that PaO_2.wmean (OR 0.992; 95%CI 0.981–1.004; P = 0.173) and prolonged hyperoxia (PaO_2.H) (OR 0.877; 95%CI 0.518-1.485; P = 0.625) were not related to in-hospital mortality in the complete sample of 419 patients. In the logistic regression using the full data while adjusting for the propensity score the odds ratio of hyperoxia for in-hospital mortality was 1.25 (95%CI 0.64–2.42; P = 0.51) without being statistically significant. The conditional logistic regression for the matched data showed that the effect of hyperoxia as nominal variable (PaO_2.H and PaO_2.N) on in-hospital mortality was not statistically significant (OR 1.46; 95%CI 0.72–2.96; P = 0.29). PaO_2.wmean (OR 1.017, 95%CI 0.9954–1.039; P = 0.124) and PaO_2.max (OR 1.003, 95%CI 0.9982–1.008; P = 0.226) were also no predictors for in-hospital mortality in the conditional logistic regression.

Discussion

Key findings

The present single centre ICU retrospective medical record audit investigated the incidence of

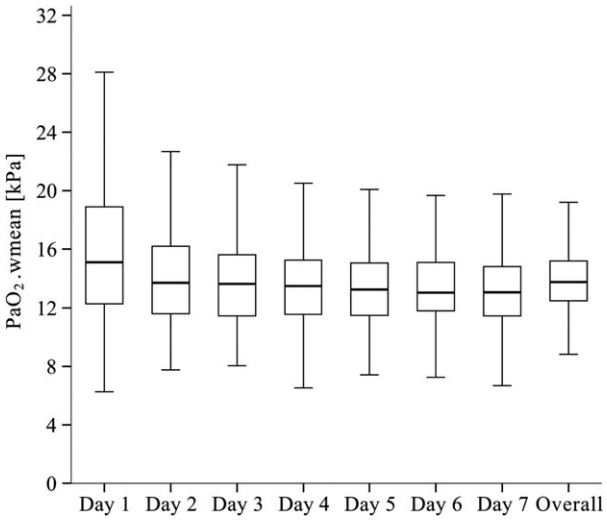

Fig. 2. Time-weighted arterial partial pressure of oxygen (PaO_2.wmean) during consecutive days of mechanical ventilation (n = 20,889 arterial blood gas analyses). Data are presented as median ± interquartile range. PaO_2.wmean was 14.0 ± 2.4 kPa and variability was highest on the first day of mechanical ventilation (interquartile range 12.3–18.9). Abbreviations: PaO_2.wmean, time-weighted mean values of arterial partial pressure of oxygen.

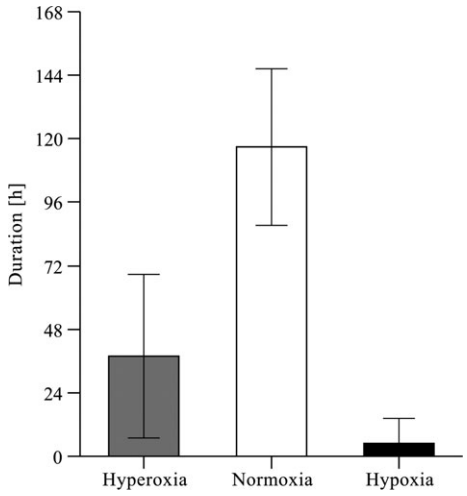

Fig. 3. Duration of hyperoxia (PaO_2 > 16 kPa), normoxia (PaO_2 8–16 kPa), and hypoxia (PaO_2 < 8 kPa) in the whole observation period (n = 20,889 arterial blood gas analyses). Data are presented as mean ± standard deviation. Results show that hyperoxia frequently occurs in ICU patients (37.9 ± 31.0 h, 23.7% of observational time).

hyperoxia and related in-hospital mortality in critically ill patients. Our study was the first investigating daily hyperoxia burden over seven consecutive days in patients undergoing IMV. PaO_2.wmean values showed the highest variability and mean on the first day of IMV on ICU. Continuous hyperoxia occurred in 23.7% of observation period. Our results demonstrated that hyperoxic episodes predominantly occurred in younger patients receiving FiO_2 levels ≤ 50%. The occurrence of hyperoxia showed no effect on in-hospital and ICU mortality, duration of ICU stay or overall hospitalization as compared to normoxia exposure.

Incidence of hyperoxia

In contrast to former studies, we did not investigate only one single PaO_2 value but calculated mean PaO_2 over time. Also, the studied ICU patients underwent IMV for at least seven consecutive days while most published research is based on first 24–48 h after ICU admission. As recently suggested by Helmerhorst et al., clinical studies investigating this topic should not only take into account solitary PaO_2 values on ICU admission but also instead investigate for time-averaged mean of PaO_2 and other values to determine hyperoxic burden of ICU patients.[9]

With the given study design, we could identify patients being exposed to hyperoxia beyond doubt. ABG results showed that intraday variability and mean PaO_2 values were highest on the first day of observation period with 184 patients (43.9%) presenting hyperoxia. This finding is similar to another study reporting 49.8% of hyperoxic patients on first day of ICU admission.[5] Only including data from the first day of admission could have been misleading on the actual exposure to hyperoxia of patients.

We could show that continuous hyperoxia, in terms of time-weighted mean of PaO_2 > 16 kPa, occurred in 23.7% during the entire observation period. These findings demonstrate that hyperoxia frequently occurs in ICU patients, despite standard operating procedures on ICU aiming for reduction in excessive O_2 levels. ICU patients are exposed to a significant hyperoxic burden over time. A recent meta-analysis published in 2014 by Damiani et al. concluded that one of the main issues in comparing literature regarding this relevant topic is the heterogeneity of ICU patients in mixed collectives, different definitions of hyperoxia (e.g., PaO_2 > 16 kPa, PaO_2 > 40 kPa), as well as selection of the values used for

Table 2 Comparison of patients with hyperoxic (PaO_2.H, PaO_2.wmean > 16 kPa) and normoxic (PaO_2.N, PaO_2.wmean 8–16 kPa) PaO_2 values from the unmatched data (†) as well as after propensity score matching (*).

	PaO_2.H matched (n = 76)	PaO_2.N matched (n = 76)	P value*	PaO_2.N unmatched (n = 343)	P value†
Age, years	43.3 (21.6)	46.2 (22.1)	0.415	57.3 (18.6)	**<0.0001**
Female, *n*	36 (47.4%)	32 (42.1%)	0.514	125 (36.4%)	0.09
SAPS2	43.1 (18.7)	42.8 (16.5)	0.901	47.4 (18.5)	0.073
PaO_2.wmean, kPa	17.7 (1.7)	14.2 (1.1)	**<0.0001**	98.7 (11.8)	**<0.0001**
PaO_2.max, kPa	49.5 (15.7)	47.1 (14.0)	0.051	31.0 (13.0)	**<0.0001**
FiO_2.wmean, %	42.8 (9.9)	44.2 (7.9)	0.348	50.7 (12.1)	**<0.0001**
Mean SaO_2, %	98.6 (1.7)	98.2 (1.2)	0.150	97.6 (1.6)	**<0.0001**
Hemoglobin, g/dl	10.0 (1.0)	9.9 (1.2)	0.375	9.9 (1.2)	0.314
Admission diagnose, *n*					
Cardiovascular	13 (17.1%)	13 (17.1%)	1	67 (19.5%)	0.747
Respiratory	25 (32.9%)	21 (27.6%)	0.597	83 (24.2%)	0.146
Gastrointestinal	7 (9.2%)	10 (13.2%)	0.608	62 (18.1%)	0.061
Neurological	20 (26.3%)	16 (21.1%)	0.567	65 (19.0%)	0.157
Other	11 (14.5%)	16 (21.1%)	0.40	66 (19.2%)	0.414
Duration of (h)					
Hypoxia	1.7 (3.1)	1.6 (2.4)	0.752	5.6 (10.2)	**<0.0001**
High FiO_2	30.9 (39.4)	41.1 (40.4)	0.535	63.2 (52.1)	**<0.0001**
In-hospital mortality, *n*	25 (32.9%)	19 (25.0%)	0.282	123 (35.9%)	0.691
ICU mortality, *n*	20 (26.3%)	17 (22.4%)	0.571	106 (30.9%)	0.491
HLOS, d	43.3 (30.2)	48.3 (33.3)	0.330	58.9 (46.9)	**0.0003**
ICU-LOS, d	24.5 (15.9)	24.5 (17.6)	0.992	30.7 (25.2)	**0.039**

Hypoxia was defined as PaO_2 < 8 kPa. Data is presented as mean (SD) and number (proportion). High FiO_2 was defined as duration in hours (SD) with FiO_2 > 50%. Bold values indicate statistical significance. ABG, arterial blood gas analysis; FiO_2, fraction of inspired oxygen; h, hour; HLOS, hospital length of stay; ICU, intensive care unit; ICU-LOS, intensive care unit length of stay; SaO_2, arterial hemoglobin oxygen saturation; SAPS2, simplified acute physiology score 2; PaO_2, arterial partial pressure of oxygen.

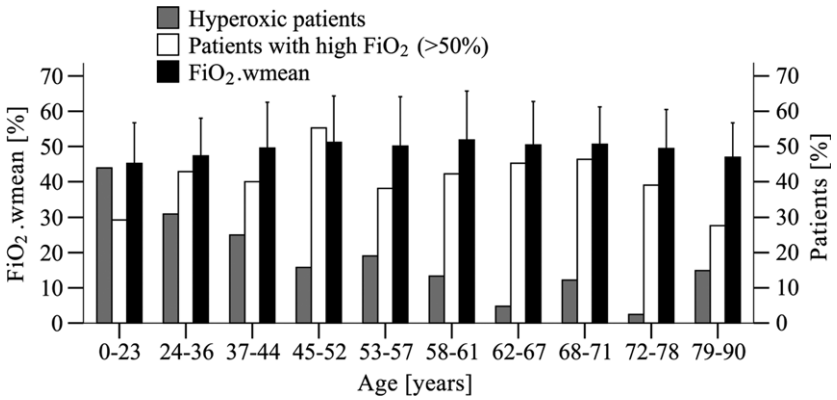

Fig. 4. Fraction of inspired oxygen (FiO_2) and observed hyperoxia in percentiles of age. Data are presented as mean ± SD or percent and are clustered by percentiles of age. Younger patients experienced higher hyperoxia burden despite lower FiO_2 levels. Abbreviations: FiO_2, fraction of inspired oxygen; FiO_2.wmean, time-weighted mean values of fraction of inspired oxygen.

investigation (e.g., worst PaO_2, highest PaO_2, mean PaO_2, time-weighted SpO_2).[6] We chose PaO_2 > 16 kPa as the threshold for hyperoxia in this study as it is more likely to find patients being exposed to hyperoxia for 7 days. Furthermore, two multicentre retrospective cohort studies also examining mixed ICU patients receiving IMV used that definition for hyperoxia, which enables us to more reliably compare our results to former studies.

Hyperoxia and in-hospital mortality

This study results did not find a correlation between hyperoxia and increased in-hospital mortality. Normoxic patients showed lower in-hospital and ICU mortality compared to hyperoxic patients, without being statistically significant. As the absolute risk reduction was close to eight percent for normoxia, this is a promising trend for following investigations with a higher number of studied patients. Also, Girardis et al. reported an absolute risk reduction of 8.6% in their conservative group targeting for lower PaO_2 and SpO_2 in ICU patients.[10] Unfortunately, they had to stop enrolling patients early and thereby missed the calculated sample size for the primary outcome ICU mortality.

Interestingly, we observed that patients with hyperoxia had shorter HLOS and ICU-LOS, potentially attributed to the fact that patients of young age predominantly experienced episodes of hyperoxia. After propensity score matching, no differences were observed anymore. Furthermore, other than expected, episodes of hyperoxia predominantly occurred at low rather than high FiO_2 settings. Our data therefore suggest that typical ICU patients at risk for hyperoxia burden might be young and less severe critically ill ICU patients receiving a lower FiO_2. We believe that this finding is of clinical interest and needs to be taken into account when tailoring for individual optimal O_2 values during IMV. In our opinion, further research investigating the beneficial or harmful effects of hyperoxia in ICU patients, especially with prolonged exposure, seems justified. Although some clinical data suggests that hyperoxia may relate to increased morbidity and mortality, the debate on the elusive promise of hyperoxia continues and further clarification is needed.

Future concepts of more tailored O_2 therapy

Recent clinical evidence suggests that ICU staff is aware of the potentially harmful effects of prolonged hyperoxia.[11,12] Nevertheless, O_2 therapy still is not often adjusted to the individual ICU patient needs for various reasons. This includes technological difficulties of tailoring for individual O_2 values but also missing consensus guidelines on optimal O_2 targets.[13–15] Despite, novel approaches for the implementation of more conservative rather than liberal O_2 targets in ICU settings were published and appear feasible and easy to implement.[16–19] One step further, Martin and Grocott et al. brought up the idea of permissive hypoxemia, meaning deliberately tailoring arterial oxygenation below normally tolerated levels to avoid hyperoxia. Still, this novel concept needs clinical testing and lacks of solid evidence to improve ICU patient outcome.[20,21]

Study limitations and strengths

One limitation of our single centre study is that the patient cohort investigated is rather small and therefore potentially underpowered. However, we did only include ICU patients with IMV for at least 7 days. Similar to former studies, we investigated a mixed anaesthesiological and surgical cohort that might bias our results. Also, we unfortunately did not investigate for the effects of hyperoxia on organ dysfunction as assessed by laboratory or clinical signs of organ injury. In the opinion of the authors it is of great clinical interest if ICU patients with reduced oxidative reserve (e.g. sepsis, diabetes, old age) might be more susceptible to oxidative injury than younger and healthier ICU patients. The potentially harmful rather than beneficial effects of hyperoxia are investigated in numerous running trials with different approaches (NCT02321072, NCT02713451, NCT02378545) showing the broad interest on this topic especially in ICU patients with severe sepsis and acute respiratory failure. Another strong limitation of this study is the assumption that PaO_2 and FiO_2 remained stable over time when calculating for time-weighted mean PaO_2 and FiO_2 values. However, performing more frequent repetitive daily ABG would be extremely time and personnel consuming and seems unrealistic to perform. Although this issue certainly represents a study limitation, we believe that our approach seems valuable to approximate hyperoxic burden and propose in accordance to Helmerhorst et al. that it should be used in further clinical studies.[9] Finally, we acknowledge that our study has been retrospective in nature and results must be interpreted with caution. An initial inhomogeneity of the study sample

was well treated by propensity score matching. After that, a representative, matched control group without hyperoxic burden was available and compensated in part for the retrospective character of the study. Demographic properties and existing comorbidities were taken into account and did not differ in the finally analysed patient data.

The quest on optimal O_2 targets in perioperative and ICU settings is not over. Oxygen is regarded a drug with dose- and time-dependent side effects. This topic is of special interest for all anaesthesiologists and intensivists and should be followed up in future trials with a prospective study design to distinctly examine the influence of elevated oxygen levels on ventilated ICU patients. The importance of oxygen titration is also reflected in the recent WHO recommendation for perioperative high FiO_2 during abdominal surgery to reduce surgical site infections,[22] which is very controversially discussed.

Conclusion

The present retrospective study investigated hyperoxia burden and associated in-hospital mortality in critically ill patients undergoing invasive mechanical ventilation for at least 7 days. Results showed that highest mean PaO_2 values and highest PaO_2 variability occurred on the first day of mechanical ventilation. Continuous hyperoxia was observed in 18.1% of patients or nearly one-fourth of time during the whole observation period. Hyperoxia occurred especially at low to moderate FiO_2 settings in younger patients with smaller SAPS2. After propensity score matching, hyperoxia was not associated with increased in-hospital mortality or ICU mortality. More evidence is needed to give clear advice on optimal individual O_2 targets in critically ill patients during IMV.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Descriptive baseline characteristics of survivors and non-survivors.