The effects of oxygen in critical illness

Helmerhorst, H.J.F.

7

METRICS OF ARTERIAL HYPEROXIA AND ASSOCIATED OUTCOMES IN CRITICAL CARE

Hendrik J.F. Helmerhorst, Derk L. Arts, Marcus J. Schultz,
Peter H.J. van der Voort, Ameen Abu-Hanna,
Evert de Jonge, David J. van Westerloo

Crit Care Med. 2017 Feb;45(2):187-195
doi: 10.1097/CCM.0000000000002084

ABSTRACT

Objective

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

Design

Observational cohort study

Setting

Three large tertiary care ICUs in the Netherlands

Patients

A total of 14,441 eligible ICU patients

Interventions

None

Measurements and Main Results

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

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

Conclusions

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

INTRODUCTION

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

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

MATERIALS AND METHODS

Data collection

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

Hyperoxia metrics

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

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

Metrics of single sampling

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

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

Metrics of central tendency

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

Metrics of cumulative exposure

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

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

Statistical Analyses

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

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

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

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

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

RESULTS

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

Metric characteristics

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

Table 1. Descriptive characteristics

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

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

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

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

Clinical outcomes

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

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

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

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

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

Subpopulations

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

DISCUSSION

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

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

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

Table 2. (continued)

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

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

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

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

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

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

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

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

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

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

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

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

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

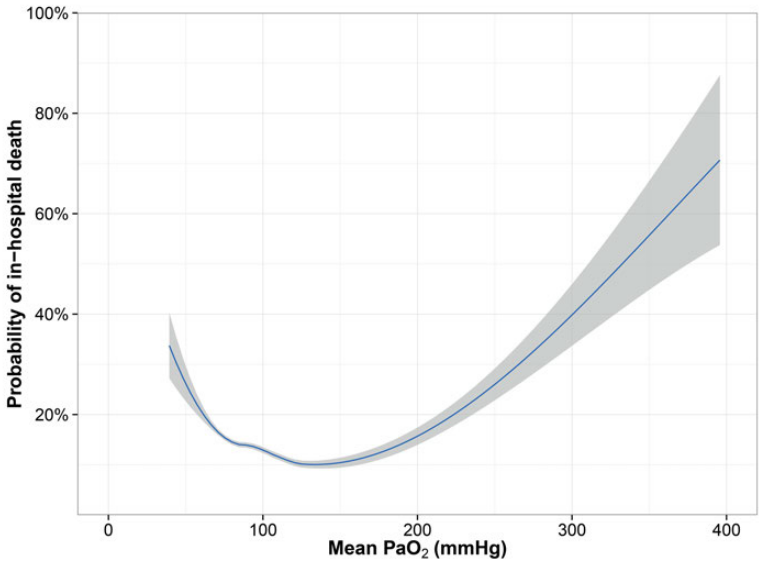

Figure 1. Adjusted probability of in-hospital death by mean PaO_2.
Loess smoothing curve predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Blue line represents oxygenation by mean PaO_2 over the total ICU LOS. Grey zones represent 95% confidence intervals.

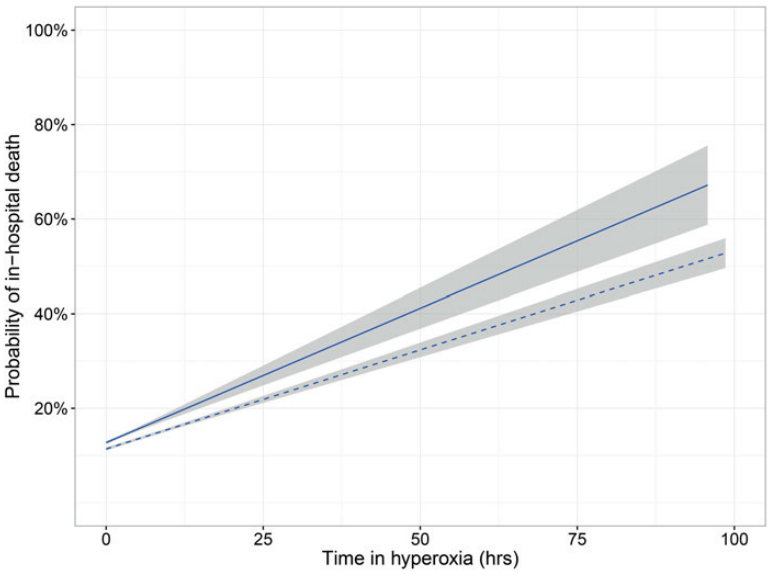

Figure 2. Adjusted probability of in-hospital death by time in hyperoxia.
Probability of death predicted from logistic regression model adjusted for age, APACHE IV score and ICU LOS. Lines represent estimated time in mild (dashed) and severe (solid) hyperoxia. Grey zones represent 95% confidence intervals.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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

ACKNOWLEDGEMENTS

Statistical comments by Dr. Ronald B. Geskus are gratefully acknowledged.

ONLINE SUPPLEMENT

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

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

REFERENCES

1. de Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E. Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO2. Intensive Care Med. 2011;37(1):46-51.
2. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. Ann Intensive Care. 2014;4:23.
3. Suzuki S, Eastwood GM, Peck L, Glassford NJ, Bellomo R. Current oxygen management in mechanically ventilated patients: a prospective observational cohort study. J Crit Care. 2013;28(5):647-54.
4. Helmerhorst HJ, Schultz MJ, van der Voort PH, de Jonge E, van Westerloo DJ. Bench-to-bedside review: the effects of hyperoxia during critical illness. Crit Care. 2015;19(1):284.
5. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation. 2015;131(24):2143-50.
6. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. Am Heart J. 2009;158(3):371-7.
7. Wang CH, Chang WT, Huang CH, Tsai MS, Yu PH, Wang AY, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation. 2014;85(9):1142-8.
8. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18(6):711.
9. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness: A Systematic Review, Meta-Analysis, and Meta-Regression of Cohort Studies. Crit Care Med. 2015;43(7):1508-19.
10. O'Driscoll BR, Howard LS. How to assess the dangers of hyperoxemia: methodological issues. Crit Care. 2011;15(3):435; author reply
11. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Wilde RB, et al. Effectiveness and Clinical Outcomes of a Two-Step Implementation of Conservative Oxygenation Targets in Critically Ill Patients: A Before and After Trial. Crit Care Med. 2016;44(3):554-63.
12. Arts D, de Keizer N, Scheffer GJ, de Jonge E. Quality of data collected for severity of illness scores in the Dutch National Intensive Care Evaluation (NICE) registry. Intensive Care Med. 2002;28(5):656-9.
13. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. Crit Care. 2008;12(6):R156.
14. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg. 2012;147(11):1042-6.
15. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med. 2012;38(1):91-8.
16. Smith PL. Splines as a Useful and Convenient Statistical Tool. American Statistician. 1979;33(2):57-62.
17. Mackenzie IM, Whitehouse T, Nightingale PG. The metrics of glycaemic control in critical care. Intensive Care Med. 2011;37(3):435-43.
18. Schoenfeld DA, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. Crit Care Med. 2002;30(8):1772-7.

19. Stolmeijer R, ter Maaten JC, Zijlstra JG, Ligtenberg JJ. Oxygen therapy for sepsis patients in the emergency department: a little less? Eur J Emerg Med. 2014;21(3):233-5.

20. Akca O. Hyperoxia: is it a biomarker for mortality? Intensive Care Med. 2015;41(10):1873-4.

21. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. Intensive Care Med. 2015;41(6):1118-21.

22. Schindler O, Gemes G, Spindelboeck W. Oxygen and cardiac arrest: the timepoint matters. Intensive Care Med. 2015;41(5):952.

23. Elmer J, Scutella M, Pullalarevu R, Wang B, Vaghasia N, Trzeciak S, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med. 2015;41(1):49-57.

24. Elmer J, Wang B, Melhem S, Pullalarevu R, Vaghasia N, Buddineni J, et al. Exposure to high concentrations of inspired oxygen does not worsen lung injury after cardiac arrest. Crit Care. 2015;19:105.

25. Helmerhorst HJ, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care. 2015;19:348.

26. Dahl RM, Gronlykke L, Haase N, Holst LB, Perner A, Wetterslev J, et al. Variability in targeted arterial oxygenation levels in patients with severe sepsis or septic shock. Acta Anaesthesiol Scand. 2015;59(7):859-69.

27. Llitjos JF, Mira JP, Duranteau J, Cariou A. Hyperoxia toxicity after cardiac arrest: What is the evidence? Ann Intensive Care. 2016;6(1):23.