Metrics of Arterial Hyperoxia and Associated Outcomes in Critical Care*

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Objective: Emerging evidence has shown the potential risks of arterial hyperoxia, but the lack of a clinical definition and methodologic 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 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 analyses, including the 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 mm Hg; severe hyperoxia as Pao_2 greater than 200 mm Hg. 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 were retrospectively analyzed using regression models in different subgroups of patients. Severe hyperoxia was associated with higher mortality rates and fewer ventilator-free days 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 physiologic 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. (*Crit Care Med* 2017; 45:187–195)

Key Words: arterial oxygenation, clinical outcomes, epidemiology, hyperoxia

Oxygen therapy and arterial oxygenation play a vital role in the clinical course of patients in the ICU. The effects of hypoxia are well established and are actively prevented in order to maintain physiologic 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

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on hospital mortality of mechanically ventilated patients, but the lack of a clinical definition of hyperoxia and methodologic limitations hamper the interpretation and clinical relevance of these studies (10). Importantly, it is unknown whether the Pa_{O_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 Pa_{O_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 hr 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, ABG analyses and concurrent ventilator settings were extracted from the patient data management system (PDMS) database (MetaVision; iMDsoft, Tel Aviv, Israel) 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 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 were 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 Pa_{O_2} (FIR), highest Pa_{O_2} (MAX), worst Pa_{O_2} (WOR), and average Pa_{O_2} (AVG), 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 (AUC), 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 occurrence rate in the present cohort. Mild hyperoxia was defined as Pa_{O_2} 120–200 mm Hg (13) and severe hyperoxia as Pa_{O_2} greater than 200 mm Hg (14).

Metrics of Single Sampling

The FIR was the Pa_{O_2} value that was measured in the first ABG registered in the PDMS after the patient was admitted to the ICU.

MAX was the maximum value that was registered during the first 24 hours ($MAX_{0–24}$) or during the total ICU length of stay (LOS) ($MAX_{ICU\ LOS}$). WOR was defined as the Pa_{O_2} derived from the ABG associated with the lowest concurrent Pa_{O_2}-to-F_{IO_2} ratio and also calculated for the first 24 hours ($WOR_{0–24}$) and over the total ICU LOS ($WOR_{ICU\ LOS}$) (13, 15).

Metrics of Central Tendency

The AVG and median Pa_{O_2} (MED) were calculated over the first 24 hours and over the total ICU LOS per admission.

Metrics of Cumulative Exposure

Per patient, the AUC was computed over the first 24 hours ($AUC_{0–24}$), first 96 hours ($AUC_{0–96}$), and total duration of ICU admission ($AUC_{ICU\ LOS}$) using linear interpolation of the available Pa_{O_2} measurements. We calculated the MED over the respective time frames and inserted these values as Pa_{O_2} measurements at the starting ($t = 0$) and endpoint 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 Pa_{O_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 mm Hg) or data distribution (quintiles) and compared these categories to normoxia (60–120 mm Hg) 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 VFDs 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 Acute

Physiology and Chronic Health Evaluation (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 FIR, AVG, MED, WOR, or MAX within the first 24 hours of admission. The multivariate models were reanalyzed by additionally adjusting for applied F_{IO_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 (interquartile range [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, http://links.lww.com/CCM/C113). 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 $WOR_{0–24}$. Cluster analysis in the Supplemental Digital Content showed that the metrics could be subdivided in multiple families, where the MAX appeared to be least related to the other metrics (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C113).

Within 24 hours of admission, a spline-based transformation of the WOR was the best discriminator for hospital mortality. When recalculating the APACHE score with different

TABLE 1. Descriptive Characteristics of Patients, Oxygenation, and Ventilation

Characteristics	Total
Patients characteristics	
No. of patients	14,441
Demographics	
Age, yr	65 (55–73)
Male, *n* (%)	9,315 (64.5)
Body mass index, kg/m^2	25.8 (23.3–29.0)
Planned admission, *n* (%)	7,328 (50.7)
Medical admission, *n* (%)	5,130 (35.5)
Planned surgery, *n* (%)	5,038 (34.9)
Emergency surgery, *n* (%)	1,344 (9.3)
Clinical characteristics	
APACHE IV score	54 (41–75)
APACHE IV predicted mortality, %	5.2 (1.4–22.9)
SAPS II	34 (26–45)
SAPS II predicted mortality, %	15 (7–34)
Clinical outcomes	
Mechanical ventilation time, hr	11 (5–40)
ICU length of stay, hr	37 (21–85)
ICU mortality, *n* (%)	1,427 (9.9)
Hospital mortality, *n* (%)	1,989 (13.8)
Oxygenation and ventilation characteristics	
No. of arterial blood gas analyses	295,079
Arterial blood gas results	
Pa_{O_2}, mm Hg	81 (70–98)
Pa_{CO_2}, mm Hg	40 (34–46)
pH	7.42 (7.36–7.47)
Hemoglobin, 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	
F_{IO_2}, %	40 (31–50)
Positive end-expiratory pressure, cm H_2O	7 (5–10)
Mean airway pressure, cm H_2O	11 (9–14)
Oxygenation measures	
Pa_{O_2}-to-F_{IO_2} ratio	219 (165–290)
Oxygenation index	3.8 (2.5–6.1)

APACHE = Acute Physiology and Chronic Health Evaluation, SAPS = Simplified Acute Physiology Score.

Data are means (± SD) or medians (interquartile range), unless stated otherwise. Oxygenation index was calculated as the F_{IO_2}-to-Pa_{O_2} ratio multiplied by the concurrent mean airway pressure.

metrics using Pao_2 data from the first 24 hours of admission, equal discrimination (*C*-statistic) was found for APACHE IV with either WOR, MAX, FIR, AVG, or MED (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C113).

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 WOR, where lower or equal mortality rates and more VFDs for severe hyperoxia were assessed (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C113).

Table 2 shows the event rates and adjusted estimates regarding patient-centered outcomes for each metric. The estimates are pooled in forest plots (**Supplemental Figs. 3** and **4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C113), 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 AVG, closely followed by the MED. 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 (**Fig. 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 (**Fig. 2**). U-shaped (FIR, $WOR_{ICU\ LOS}$, and

TABLE 2. Event Rates and Adjusted Estimates for Patient-Centered Outcomes by Metric of Arterial Hyperoxia

Variable	No. of Patients (%)	Deaths (%)	Hospital Mortality[a] OR (95% CI)	ICU Mortality[a] OR (95% CI)	Ventilator-Free Days and Alive at Day 28[b] Mean Difference (95% CI)
First Pao_2	14,441				
Mild hyperoxia[c]	4,144 (29)	440 (11)	0.91 (0.79–1.05)	0.92 (0.78–1.09)	0.29 (−0.02 to 0.59)
Severe hyperoxia[c]	1,582 (11)	262 (17)	1.11 (0.92–1.34)	1.06 (0.85–1.31)	−0.10 (−0.54 to 0.33)
$AVG_{ICU\ LOS}$	14,441				
Mild hyperoxia[c]	2,142 (15)	223 (10)	1.12 (0.93–1.34)	1.35 (1.09–1.67)[d]	0.32 (−0.06 to 0.69)
Severe hyperoxia[c]	131 (1)	45 (34)	3.79 (2.32–6.14)[e]	5.93 (3.56–9.77)[e]	−3.38 (−4.81 to −1.94)[e]
$MED_{ICU\ LOS}$	14,441				
Mild hyperoxia[c]	1,502 (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)[d]	3.76 (1.93–7.09)[e]	−1.50 (−3.26 to 0.25)
$WOR_{ICU\ LOS}$	14,062				
Mild hyperoxia[c]	1,316 (9)	65 (5)	0.71 (0.52–0.95)	0.65 (0.44–0.93)	0.73 (0.29–1.17)[d]
Severe hyperoxia[c]	86 (1)	8 (9)	1.29 (0.48–3.05)	2.06 (0.74–4.97)	−0.54 (−2.24 to 1.16)
$MAX_{ICU\ LOS}$	14,441				
Mild hyperoxia[c]	5,986 (41)	745 (12)	1.07 (0.93–1.23)	0.96 (0.81–1.14)	−0.49 (−0.80 to −0.19)[d]
Severe hyperoxia[c]	2,854 (20)	679 (24)	1.74 (1.49–2.03)[e]	1.92 (1.61–2.30)[e]	−2.29 (−2.66 to −1.91)[e]
$AUC_{ICU\ LOS}$	14,049				
Fourth quintile[f]	2,810 (20)	451 (16)	1.27 (1.04–1.54)	1.24 (0.98–1.57)	NA
Upper quintile[f]	2,810 (20)	788 (28)	1.45 (1.18–1.78)[g]	1.28 (1.01–1.63)	NA
$AVG_{0–24}$	14,425				
Mild hyperoxia[c]	2,896 (20)	384 (13)	1.14 (0.98–1.32)	1.12 (0.94–1.33)	0.02 (−0.31 to 0.35)
Severe hyperoxia[c]	168 (1)	49 (29)	2.55 (1.62–3.94)[e]	3.14 (1.95–4.99)[e]	−1.85 (−3.10 to −0.61)[d]

(*Continued*)

TABLE 2. (*Continued*). Event Rates and Adjusted Estimates for Patient-Centered Outcomes by Metric of Arterial Hyperoxia

Variable	No. of Patients (%)	Deaths (%)	Hospital Mortality[a] OR (95% CI)	ICU Mortality[a] OR (95% CI)	Ventilator-Free Days and Alive at Day 28[b] Mean Difference (95% CI)
$MED_{0–24}$	14,425				
Mild hyperoxia[c]	2,090 (14)	237 (11)	1.10 (0.92–1.31)	1.09 (0.88–1.34)	0.16 (−0.21 to 0.54)
Severe hyperoxia[c]	122 (1)	31 (25)	2.49 (1.44–4.20)[g]	2.60 (1.42–4.61)[d]	−1.27 (−2.78 to 0.23)
$WOR_{0–24}$	14,046				
Mild hyperoxia[c]	1,556 (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 to 0.70)
$MAX_{0–24}$	14,425				
Mild hyperoxia[c]	5,617 (39)	674 (12)	0.89 (0.78–1.02)	0.87 (0.74–1.02)	0.33 (0.03–0.62)
Severe hyperoxia[c]	2,384 (17)	482 (20)	1.23 (1.05–1.44)[d]	1.29 (1.08–1.54)[d]	−0.39 (−0.78 to −0.01)
$AUC_{0–24}$	8,646				
Fourth quintile[f]	1,729 (20)	316 (18)	0.99 (0.81–1.21)	0.97 (0.77–1.22)	−0.04 (−0.68 to 0.60)
Upper quintile[f]	1,729 (20)	359 (21)	1.29 (1.06–1.57)	1.30 (1.04–1.63)	−0.45 (−1.09 to 0.18)
$AUC_{0–96}$	3,083				
Fourth quintile[f]	616 (20)	170 (28)	1.20 (0.92–1.57)	1.07 (0.79–1.43)	NA
Upper quintile[f]	617 (20)	185 (30)	1.45 (1.11–1.90)[d]	1.13 (0.84–1.53)	NA
Time in mild hyperoxia					
Upper quintile[h]	2,810 (20)	584 (21)	1.25 (1.06–1.50)[d]	1.10 (0.89–1.35)	NA
Time in severe hyperoxia					
Upper quintile[i]	2,810 (20)	415 (16)	1.31 (1.12–1.53)[g]	1.66 (1.39–1.99)[e]	NA

AUC = area under curve of Pao_2 measurements in considered time frame, AVG = mean Pao_2, LOS = length of stay, MAX = highest Pao_2, MED = median Pao_2, NA = not applicable according to used model, OR = odds ratio, WOR = worst Pao_2.

[a]Model is adjusted for age, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, and ICU length of stay.

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

[c]Arterial normoxia (Pao_2, 60–120 mm Hg) used as reference range.

[d]$p < 0.01$.

[e]$p < 0.0001$.

[f]Middle quintile (area under the curve) used as reference range.

[g]$p < 0.001$.

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

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

Metrics are calculated over the total ICU length of stay, over the first 24 hr of ICU admission (0–24) or over the first 96 hr of admission (0–96), as indicated. Some patients were excluded for specific metric analyses if there were no requisite data within the first 24 hr of admission (0–24 subgroups), if there were no data on Pao_2-to-Fio_2 ratio (worst Pao_2) or if there was an interval longer than 24 hr between two consecutive Pao_2 measurements (area under the curve and time spent in hyperoxia). Mild hyperoxia: Pao_2, 120–200 mm Hg; severe hyperoxia: Pao_2, > 200 mm Hg. Hospital and ICU mortality refer to mortality, given either death or discharge (conditional hospital mortality).

$MED_{ICU\ LOS}$) and linear ($MAX_{ICU\ LOS}$) relationships were found for the other metrics (**Supplemental Figs. 5–8**, Supplemental Digital Content 1, http://links.lww.com/CCM/C113).

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 supraphysiologic arterial oxygen levels and hospital mortality, ICU mortality and VFDs. The effect size

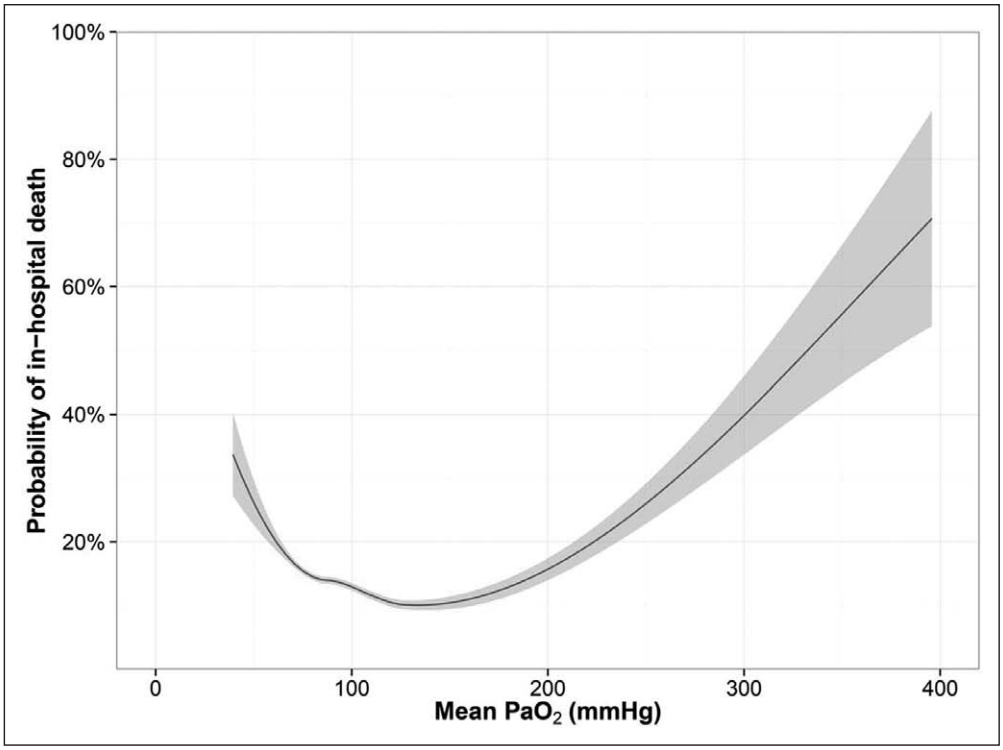

Figure 1. Adjusted probability of in-hospital death by mean Pao_2. Loess smoothing curve predicted from logistic regression model adjusted for age, Acute Physiology and Chronic Health Evaluation IV score, and ICU length of stay (LOS). *Solid line* represents oxygenation by mean Pao_2 over the total ICU LOS. *Gray zones* represent 95% CIs.

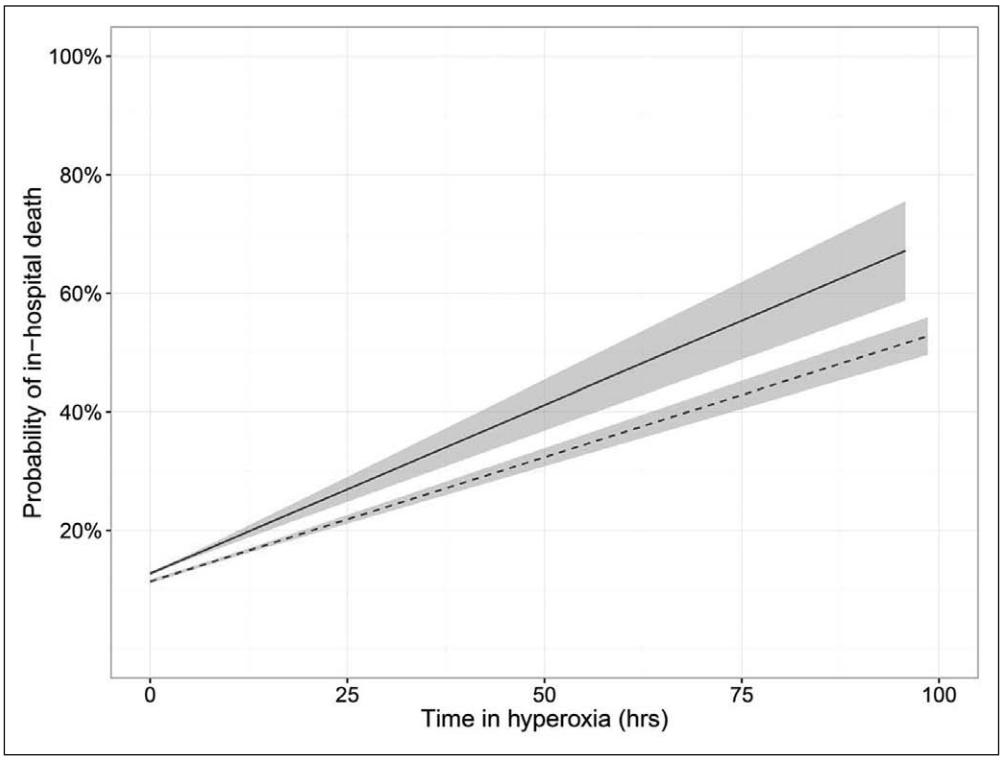

Figure 2. Adjusted probability of in-hospital death by time in hyperoxia. Probability of death predicted from logistic regression model adjusted for age, Acute Physiology and Chronic Health Evaluation IV score, and ICU length of stay. *Lines* represent estimated time in mild (*dashed*) and severe (*solid*) hyperoxia. *Gray zones* represent 95% CIs. 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.

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 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 preexisting 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 and median) were found to have the strongest relationship with outcome. The effects were smaller for the metrics of single measurements (i.e., highest, worst, and 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

TABLE 3. Arterial Hyperoxia and Adjusted Odds Ratios (95% CI) for Hospital Mortality by Subpopulation

Variable	Mechanical Ventilation	Planned Admission	Medical Admission	Cardiac Arrest	Stroke	Sepsis
No. of patients (%)	11,934 (82.6)	7,328 (50.7)	5,130 (35.5)	673 (4.7)	406 (2.8)	548 (3.9)
Deaths (%)	1,746 (14.6)	241 (3.3)	1,410 (27.5)	316 (47.0)	146 (36.0)	183 (33.4)
First Pao_2						
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)
Mean Pao_2						
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)[b]	1.74 (0.10–9.41)	4.00 (2.16–7.48)[b]	3.24 (0.84–16.57)	3.85 (0.91–19.11)	NA
Median Pao_2						
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
Worst Pao_2						
Mild hyperoxia[a]	0.63 (0.46–0.85)[c]	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
Highest Pao_2						
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)[b]	2.10 (1.44–3.06)[d]	1.78 (1.47–2.17)[b]	2.14 (1.32–3.49)[c]	0.96 (0.49–1.91)	1.03 (0.55–1.93)
Time in mild hyperoxia						
Upper quintile[e]	1.36 (1.14–1.63)[d]	1.52 (0.99–2.34)	1.35 (1.11–1.64)[c]	1.45 (0.88–2.39)	0.66 (0.32–1.35)	1.18 (0.65–2.14)
Time in severe hyperoxia						
Upper quintile[f]	1.36 (1.15–1.61)[d]	1.75 (1.21–2.52)[c]	1.57 (1.28–1.94)[b]	1.59 (0.98–2.58)	0.68 (0.36–1.25)	0.71 (0.35–1.40)

NA = not available (not enough patients in specific subset).

[a]Normoxia (Pao_2, 60–120 mm Hg) used as reference range.

[b]$p < 0.0001$.

[c]$p < 0.01$.

[d]$p < 0.001$.

[e]Zero time in mild hyperoxia is used as reference range.

[f]Zero time in severe hyperoxia is used as reference range.

All shown metrics are calculated over the total ICU length of stay. Mild hyperoxia: Pao_2, 120–200 mm Hg; severe hyperoxia: Pao_2, > 200 mm Hg. Models are adjusted for age, Acute Physiology and Chronic Health Evaluation IV score, and ICU length of stay. Hospital mortality refers to mortality, given either death or discharge (conditional hospital mortality).

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 (23, 24) to show associations with morbidity and mortality after cardiac arrest. 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, for example, 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 LOS 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 WOR 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 WOR is an important measure over the total ICU stay, but within the first 24 hours, a hypoxic WOR 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, methodologic 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 are 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 was not computed based on the total ICU LOS. The inherent limitation of noncontinuous Pa_{O_2} sampling with a lack of data between successive measurements was overcome by using linear and natural spline interpolation between separate Pa_{O_2} measurements and calculate AUCs and time spent in arterial hyperoxia, but it should be considered that real data of unmeasured arterial oxygenation and ventilatory management were 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 metaregression 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 Pa_{O_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 LOS, mechanical ventilation time, and VFDs. Our strategies to investigate the effects of a continuously changing variable on patient-centered outcomes can be further applied as a toolbox for other clinical challenges such as glucose and Co_2 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. Pa_{O_2} levels exceeding 200 mm Hg were not only associated with ICU mortality and hospital mortality but may also lead to fewer VFDs. 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 Pa_{O_2} is not a single indicator of blood oxygen and may embrace both care given and the consequences of that care. The curvilinear relationship between the metrics and outcome suggest that both arterial hypoxia and arterial hyperoxia should be actively avoided, and deviations from the normal may be a result of unfavorable oxygen management. Given the diversity of patients, clinical scenarios, and characteristics of oxygen, universal recommendations remain cumbersome. However, in expectation of future randomized controlled trials, our findings may be auxiliary to guide targeted oxygen management by estimating the potential risk in different clinical situations.

CONCLUSIONS

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

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