Original Article

Impact of hyperoxemia on mortality in critically ill patients with ventilator-associated pneumonia

Sophie Six[1,2], Anahita Rouzé[1], Olivier Pouly[1,2], Julien Poissy[1,2], Frédéric Wallet[3], Sébastien Preau[1], Saad Nseir[1,2]

[1]CHU Lille, Centre de Réanimation, Lille, France; [2]Univ. Lille, Faculté de Médecine, Lille, France; [3]CHU Lille, Centre de Biologie-Pathologie, Lille, France

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Correspondence to: Prof. Saad Nseir. CHU Lille, Centre de Réanimation, F-59000 Lille, France. Email: s-nseir@chru-lille.fr.

Background: The objective of this study was to assess the impact of hyperoxemia on mortality in critically ill patients with ventilator-associated pneumonia (VAP).

Methods: This observational study was performed in a 50-bed mixed intensive care unit (ICU) during a 1-year period. Quantitative microbiological confirmation was required for VAP diagnosis. Hyperoxemia was defined as peripheral capillary oxygen saturation (SpO_2) ≥98%. SpO_2 was hourly collected in all study patients during the whole period of mechanical ventilation. The primary objective was to assess the influence of hyperoxemia on ICU mortality.

Results: Ninety-three patients with VAP were all included in this study. ICU-mortality rate was 32% (30 of 93 patients). The mean percentage of time spent with hyperoxemia in survivors and nonsurvivors at ICU admission, before, after or at the time of VAP diagnosis was not significantly different. Multivariate analysis identified age, and sequential organ dysfunction assessment at the day of VAP occurrence as independent risk factors for ICU mortality [odds ratio (OR) =1.04 (95% CI, 1.01–1.08) per year, P=0.019; 1.19 (95% CI, 1.06–1.34) per point, P=0.003; respectively]. The time spent with hyperoxemia before VAP occurrence was not significantly associated with mechanical ventilation free days, or ICU length of stay.

Conclusions: Hyperoxemia at ICU admission, or during ICU stay, had no significant impact on ICU mortality in critically ill patients with VAP.

Keywords: Hyperoxemia; ventilator-associated pneumonia (VAP); mortality; critical illness; mechanical ventilation (MV)

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Introduction

Oxygen is commonly used in critically ill patients (1). Several studies clearly demonstrated that oxygen was frequently used beyond patients' needs and that hyperoxemia was common in the intensive care units (ICU) (2-4). However, the safety of hyperoxemia has been recently challenged (5). A strategy based on liberal oxygen treatment is meant to avoid hypoxia and increase the oxygen supply to the different suffering organs. However, this excessive supply is not safe and could generate harm via the production of reactive oxygen species (ROS). High concentrations of stress-mediated ROS can lead to cellular necrosis and apoptosis (6). Further, hyperoxemia induces vasoconstriction, and decreases cardiac output which reduces blood flow and ultimately oxygen transport (5,7). The process of oxidative stress could result in multiorgan failure (8). The association between mortality and hyperoxemia was also reported by retrospective

studies performed in different patient populations (9-11). In mechanically ventilated patients, the results of available studies on the relationship between mortality and hyperoxemia are controversial. A recent prospective study (12) evaluated the impact of conservative versus conventional oxygen therapy on mortality in ICU patients. The authors concluded that reaching a conservative oxygenation target [arterial oxygen tension (PaO_2) between 70 and 100 mmHg, or peripheral oxygen pulse saturation (SpO_2) values between 94% and 98%] resulted in decreased ICU-mortality, but the rate of patients with ventilator-associated respiratory infections was similar in the two groups.

The pathophysiology of pulmonary lesions resulting from hyperoxemia has clearly been described in animal studies (13,14). Hyperoxic acute lung injury (HALI) was reported to by previous studies. Some mechanisms responsible for HALI are similar to those of acute respiratory distress syndrome (ARDS) (15,16). Complications of hyperoxemia, such as acute lung injury, atelectasis, and decreased clearance of bacteria could be associated with the development of ventilator-associated pneumonia (VAP) (17). Entezari *et al.* (18) demonstrated that exposure to hyperoxemia for a long period of time reduced the capacity of macrophages in phagocytosing *Pseudomonas aeruginosa*. Another study reported high mortality rates in mice infected with *P. aeruginosa* and exposed to hyperoxemia (19). Recently, we performed a retrospective analysis of prospectively collected data in a cohort of 503 patients receiving mechanical ventilation (MV) for >48 h (20). The multivariate analysis identified hyperoxemia as an independent risk factor for VAP {odds ratio (OR) =1.1 [95% confidence interval (CI), 1.04–1.2] per day, P=0.004}.

To our knowledge, no clinical study has assessed the impact of hyperoxemia on mortality in patients with VAP. However, patients with VAP have located or diffuse alveolar damage, and could be at higher risk for mortality in presence of hyperoxemia. Our hypothesis was that in patients with VAP, hyperoxemia could be associated with higher ICU-mortality rates. Therefore, we conducted this single-center retrospective study to investigate the influence of hyperoxemia on ICU mortality, and morbidity in patients with VAP.

Methods

Study characteristics

This study was performed in a 50-bed mixed ICU, at the university hospital of Lille, France, from January 2016 to January 2017. The IRB of the Lille University Hospital approved the study and waived informed consent. In accordance with the French law, and because of the retrospective observational design, written informed consent was not required.

All data were retrospectively collected. All patients with VAP were included in this study. Only first VAP episodes were investigated.

Definitions

VAP was defined as the presence, >48 h after starting invasive MV, of new or progressive pulmonary infiltrate, and at least two of the following criteria: (I) fever (≥38 ℃) or hypothermia (≤36 ℃); (II) leukocytosis ($\geq 11\times10^9$/L) or leukopenia ($<3.5\times10^9$/L), and (III) purulent respiratory secretions (21). Microbiological confirmation was required in all patients [positive bronchoalveolar lavage $\geq10^4$ colony forming unit per milliliter (CFU/mL), or positive tracheal aspirate $\geq10^5$ CFU/mL]. VAP was considered as early-onset when it was diagnosed before the fifth day, and late-onset when it was diagnosed the fifth day or later, after starting MV (21).

The following microorganisms were defined as multidrug-resistant bacteria (MDRB): ceftazidime or imipenem-resistant *P. aeruginosa*, β-lactamase-producing Gram-negative bacilli, imipenem-resistant *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus*.

Hyperoxemia was defined as peripheral oxygen saturation (SpO_2) values ≥98%. In all patients, one measurement per hour was prospectively and automatically collected, during the whole period of invasive MV. The daily percentage of time spent with hyperoxemia was calculated as the number of hours with hyperoxemia divided by 24. For example, a patient who spent 6 h with hyperoxemia per day had a percentage of 25% (6/24).

Prior antibiotic use was defined as antimicrobial treatment during the three months preceding ICU admission. Antibiotic treatment was considered appropriate when at least one antibiotic active *in vitro* on all organisms causing VAP was administrated to treat VAP. Antibiotic treatment for patients with suspected VAP was based on ATS/IDSA guidelines (21).

The primary objective was to determine the impact of hyperoxemia on ICU mortality. Secondary objective was to determine the impact of hyperoxemia on duration of MV, mechanical-ventilation free days, sepsis related organ failure

assessment (SOFA) score at VAP occurrence, and length of ICU stay.

Study patients

A VAP prevention strategy was routinely used during the study period. No written guidelines regarding oxygen therapy were used in the ICU during the study period.

Data collection

All data were retrospectively recorded from January 1st, 2016 to January 1st, 2017. The followings characteristics were recorded at ICU admission: age, male gender, severity of illness based on simplified acute physiology score (SAPS) II, and SOFA score; comorbidities [diabetes, chronic obstructive pulmonary disease (COPD), chronic heart failure, cirrhosis, chronic renal failure requiring dialysis, immunosuppression], location before ICU admission, admission category (medical or chirurgical), cause of ICU admission, PaO_2, FiO_2, and percentage of time spent with hyperoxemia during the first 24 h. During ICU stay, the following data were collected: daily percentage of time spent with hyperoxemia ($SpO_2 \geq 98\%$), number of days from starting invasive MV to VAP occurrence, clinical pulmonary infection score (CPIS) and SOFA score at the day of VAP diagnosis, MV duration, microbiological results, appropriateness of antimicrobial and its duration, and ICU mortality. All data were collected from ICU admission until death or ICU discharge.

Statistical analysis

SPSS software (SPSS, Chicago, IL, USA) was used for data analysis. Categorical variables were described as frequencies (%). The distribution of continuous variables was tested for normality. Normally and skewed continuous variables were described as mean ± SD, or median and interquartile range (IQR), respectively. All P values were two-tailed. Differences were considered significant if P values were <0.05.

In order to determine factors associated with mortality, survivors were compared with nonsurvivors using bivariate and multivariate analyses. The χ^2 test or Fischer's exact test were used to compare qualitative variables, as appropriate. Student's *t*-test or the Mann-Whitney U-test were used to compare continuous variables, as appropriate. All variables from univariate analysis with P values <0.1 were incorporated into the multivariate logistic regression analysis. This cut-off was set to include a limited number of variables in the logistic regression model, as the number of outcomes (death in the ICU) was relatively small (n=30). The OR and 95% CI were calculated for all significant qualitative variables in univariate analysis, and all significant variables in multivariate analysis. Potential interactions were tested, and the Hosmer-Lemeshow goodness-of-fit was calculated. The multivariable model was considered as accurate if p value of the Hosmer-Lemeshow test was not significant.

In order to determine the impact of hyperoxemia on morbidity, MV-free days, length of ICU stay, SOFA score at VAP diagnosis were compared between patients who spent >43% of time with hyperoxemia to those who spent ≤43% of time with hyperoxemia. The threshold of 43% was selected because it was the median time spent with hyperoxemia during the 3 days preceding VAP diagnosis in all study patients.

Results

Patient characteristics

Five hundred forty-seven patients received invasive MV for more than 48 hours during the study period. Ninety-three patients (17%) developed at least one VAP episode and were all included in the study. The incidence rate of VAP was 11.7 VAP per 1,000 ventilator-days. Thirty patients with VAP (32%) died in the ICU. Patient characteristics are presented in *Tables 1*,*2*.

Risk factors for ICU-mortality

Univariate analysis

Although age, and SOFA score at the day of VAP diagnosis were significantly lower, percentage of patients with appropriate antibiotic treatment was significantly higher in survivors, compared with nonsurvivors (*Tables 1*,*2*).

No significant difference was found in time spent with hyperoxemia at ICU admission, at VAP diagnosis, during the 7 days before VAP diagnosis, and the 7 days following VAP diagnosis between survivors and nonsurvivors (*Figure 1*).

Multivariate analysis

Age and SOFA score at VAP diagnosis were independently associated with higher risk for ICU mortality (*Table 3*).

Table 1 Characteristics of study patients at ICU admission

Variables	Survivors (n=63)	Nonsurvivors (n=30)	P value
Age, years	58 [40, 67]	62 [52, 71]	0.046
Male gender	35 [56]	22 [73]	0.100
SAPS II	57 [48, 71]	49 [42, 74]	0.399
SOFA score	8 [5, 10]	8 [5, 11]	0.843
Respiratory system	2 [2, 3]	3 [2, 4]	0.045
Nervous system	2 [1, 4]	3 [1, 3]	0.770
Cardiovascular system	0 [1, 4]	0 [0, 4]	0.970
Liver	0 [0, 0]	0 [0, 1]	0.093
Coagulation	0 [0, 0]	0 [0, 1]	0.340
Kidneys	0 [0, 2]	0 [0, 3]	0.940
Comorbidities			
Diabetes	16 [25]	9 [30]	0.640
COPD	7 [11]	8 [27]	0.057
Cardiac failure	6 [10]	5 [17]	0.319
Cirrhosis	4 [6]	4 [13]	0.261
Chronic kidney failure	5 [8]	2 [7]	0.828
Immunodeficiency	17 [27]	10 [33]	0.528
Location before ICU admission			0.549
Home	26 [41]	9 [30]	
Other wards	25 [40]	15 [50]	
Other ICUs	12 [19]	6 [20]	
Cause for ICU admission			
Acute exacerbation of COPD	4 [6]	2 [7]	0.954
Respiratory acute failure	11 [17]	4 [13]	0.767
Community-acquired pneumonia	9 [14]	6 [20]	0.484
Nosocomial pneumonia	11 [17]	6 [20]	0.767
ARDS	7 [11]	1 [3]	0.430
Cardiac arrest	5 [8]	2 [7]	0.828
Neurologic failure	20 [32]	5 [17]	0.142
Poisoning	5 [8]	0 [0]	0.171
Septic shock	14 [22]	8 [27]	0.637
Cellulitis	3 [5]	3 [10]	0.383
Prior antimicrobial treatment	56 [89]	27 [90]	0.872
Percentage of time spent with hyperoxemia, mean ± SD	44±21	48±23	0.590
Results of blood gases			
PaO_2, mmHg	116 [85, 173]	112 [80, 172]	0.493
PaO_2 >120 mmHg	31 [49]	13 [43]	0.551
PaO_2/FiO_2	192 [133, 287]	171 [118, 252]	0.410

Data are presented as n [%] or median [interquartile range], unless otherwise indicated. SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ARDS, acute respiratory distress syndrome; PaO2, partial pressure of arterial oxygen; FiO_2, fraction of inspired O_2.

Table 2 Patient characteristics during ICU stay

Characteristics	Survivors (n=63)	Nonsurvivors (n=30)	P value
At VAP diagnosis			
Early-onset VAP	19 [30]	8 [27]	0.729
Duration of mechanical ventilation before VAP occurrence	9 [5, 15]	9 [5, 18]	0.522
Appropriate antibiotic treatment	62 [98]	26 [87]	0.019*
Duration of prior antimicrobial treatment, d	7 [3, 13]	8 [6, 11]	
SOFA score	5 [4, 9]	8 [6, 13]	0.005
Respiratory system	2 [2, 3]	3 [3, 4]	0.045
Nervous system	1 [1, 3]	2 [1, 3]	0.071
Cardiovascular system	0 [0, 1]	3 [0, 4]	0.009
Liver	0 [0, 0]	0 [0, 2]	0.085
Coagulation	0 [0, 1]	0 [0, 2]	0.025
Kidneys	0 [0, 1]	0 [0, 2]	0.038
CPIS	9 [7, 10]	9 [8, 11]	0.117
Percentage of time spent with hyperoxemia, mean ± SD	40±30	40±34	0.647
During ICU stay			
Total duration of antimicrobial treatment	18 [11, 28]	17 [14, 26]	0.856
Duration of mechanical ventilation	24 [13, 48]	26 [16, 43]	0.851
Length of ICU stay	29 [20, 61]	25 [15, 47]	0.291
Percentage of time spent with hyperoxemia during the 7 days preceding VAP, mean ± SD	48±28	45±23	0.731
Percentage of time spent with hyperoxemia during the 7 days subsequent to VAP, mean ± SD	48±24	40±24	0.167

Data are presented as n [%] or median [interquartile range], unless otherwise indicated. *, OR (95% CI): 0.10 (0.01–0.98). VAP, ventilator-associated pneumonia; SOFA, sequential organ failure assessment; CPIS, clinical pulmonary infection score; ICU, intensive care unit.

Impact of hyperoxemia on other outcomes

No significant difference was found in SOFA score at the day of VAP diagnosis, total duration of MV, MV-free days, or ICU length of stay between patients who spent >43% of time with hyperoxemia, and those who spent ≤43% of time with hyperoxemia during the 3 days preceding VAP occurrence (*Table 4*).

Microbiological results

VAP was polymicrobial in 15 (16%) patients, and related to MDRB in 25 (27%) patients. Gram-negative bacteria represented 78% of all bacteria, and were identified in 75% of VAP patients. *P. aeruginosa* (24%), *Klebsiella sp.* (16%), and *S. aureus* (18%) were the most common bacteria in VAP patients (*Table 5*).

Discussion

In our study, hyperoxemia at ICU admission, or during ICU stay, was not significantly associated with ICU mortality in VAP patients. Similarly, hyperoxemia did not impact morbidity (duration of MV, MV-free days, SOFA score at VAP occurrence, and length of ICU stay) in these patients. Only age and SOFA score at the day of VAP occurrence

were independently associated with higher risk for ICU mortality.

To our knowledge, our study is the first to evaluate the relationship between hyperoxemia and mortality in VAP patients. One could argue that hyperoxemia would have resulted in more severe pulmonary lesions in patients with VAP, and higher mortality rates. Previous studies have clearly shown the negative impact of hyperoxemia on the lung, and described HALI (11,13,15,16,22,23). However, no significant relationship was found between hyperoxemia and mortality in this cohort of VAP patients.

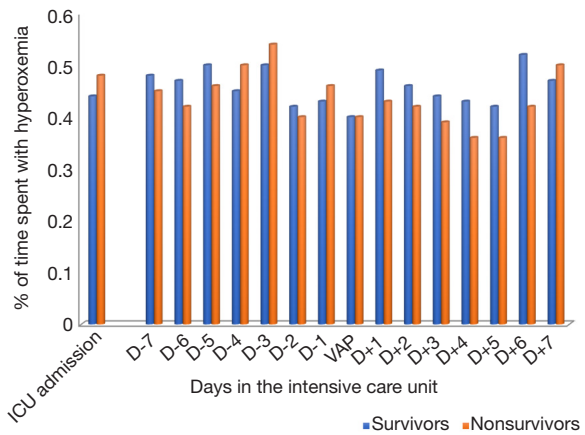

Figure 1 Relationship between hyperoxemia and ICU-mortality at ICU admission, and during ICU stay. P>0.2 for all comparisons of mean percentage of time spent with hyperoxemia between survivors and nonsurvivors.

Table 3 Factors associated with mortality by multivariate analysis

Factors	P value	OR (95% CI)
Age	0.019	1.04 (1.01–1.08)*
SOFA	0.003	1.19 (1.06–1.34)**
Appropriate antibiotic treatment	0.081	–

*, per year; **, per point of SOFA score. Hosmer-Lemshow goodness-of-fit, P=0.932. SOFA, sequential organ failure assessment; OR, odds ratio, CI, confidence interval.

The definition used for hyperoxemia was based on an arbitrary threshold and could be a matter for debate, as no consensus exists on the definition of this condition. However, the definition used in our study was rather stringent and the mean daily time spent with hyperoxemia (45%) was in line with that reported by a recent multicenter study (59%) (2). Recent interventional studies also used the threshold of SpO_2 ≥98% to define hyperoxemia (12,24-26). Only one SpO_2 value per hour was collected and we considered this value as a surrogate for the whole hour. This might have influenced the reliability of our analysis. However, this approximation could probably reflect the daily hyperoxemia exposure. In addition, no significant difference was found in percentage of patients with hyperoxemia, defined as PaO_2 >120 mmHg, at ICU admission between survivors and nonsurvivors. The arbitrary threshold of 43% of time spent with hyperoxemia was used to determine the impact of hyperoxemia on secondary outcomes. Different results would have been obtained if PaO_2 values have been used. However, all analyses were repeated using a more stringent threshold for percentage of time spent with hyperoxemia (>75th quartile) at ICU admission, at VAP diagnosis, during the 7 days preceding or following VAP. Similar results were found regarding the relationship between hyperoxemia, mortality or secondary outcomes (data not shown). In a large multicenter cohort study, a dose-response relationship was found between supraphysiological arterial oxygen levels and

Table 4 Impact of hyperoxemia on secondary outcomes

Outcomes	Percentage of time spent with hyperoxemia >43%		P value
	Yes (n=47)	No (n=46)	
Duration of mechanical ventilation, days	25 [16, 46]	22 [11, 46]	0.412
Mechanical-ventilation free days	3 [0, 10]	5 [0, 10]	0.942
SOFA score at VAP occurrence	5 [4, 10]	7 [4, 10]	0.269
Length of ICU stay, days	30 [22, 53]	29 [17, 52]	0.410

Data are presented median [interquartile range]. SOFA, sequential organ failure assessment; VAP, ventilator-associated pneumonia; ICU, intensive care unit.

Table 5 Microorganisms responsible for ventilator-associated pneumonia

Microorganisms	Value (n=116)
Gram-negative bacilli	91 [78]
Pseudomonas aeruginosa	28 [24]
Klebsiella sp.	18 [16]
Escherichia coli	11 [9]
Enterobacter sp.	9 [8]
Stenotrophomonas maltophilia	6 [5]
Heamophilus influenzae	6 [5]
Serratia sp.	3 [3]
Proteus mirabilis	3 [3]
Acinetobacter baumannii	2 [2]
Citrobacter sp.	2 [2]
Moraxella catarrhalis	1 [1]
Morganella morganii	1 [1]
Burkholderia dolosa	1 [1]
Gram-positive cocci	17 [15]
Methicillin-sensitive *S. aureus*	13 [11]
Methicillin-resistant *S. aureus*	4 [3]

Results are presented as n [%].

hospital mortality, ICU mortality, and MV-free days (11). The effect size was influenced by the definition of arterial hyperoxia, and severe hyperoxia was associated with poor outcomes.

A large number of patients included in our study had pulmonary lesions at ICU admission. Therefore, the impact of hyperoxemia on mortality could have been confounded by this factor. However, subgroup analyses of patients with or without acute lung injury at ICU admission showed similar results (data not shown). The median time from admission to VAP occurrence was relatively long (9 days). Therefore, the impact of hyperoxemia at ICU admission on mortality could have been reduced. Several previous studies showed that the negative impact of hyperoxemia on outcome was higher during the first 24 h after ICU admission, when acute illness is more severe, compared with subsequent period of MV and critical illness. The number of included patients (n=93) was relatively small. Therefore, larger studies are required to evaluate the relationship between hyperoxemia and mortality in VAP patients.

Several animal studies highlighted the relationship between hyperoxemia and VAP, and suggested that it could be related to an alteration of phagocytosis and innate immunity via molecular mechanisms and increased inflammatory response (19,27,28). In fact, in animals exposed to hyperoxemia ROS mediate both direct and indirect modulation of signaling molecules such as protein kinases, transcription factors, receptors, and pro- and anti-apoptotic factors (29). However, several aspects are unclear. Is it a concentration or a time dependent phenomenon? When hyperoxic injury is the most deleterious? How to differentiate lung injury related to MV from that associated to hyperoxemia? A better understanding of the signaling pathways leading to HALI would be helpful to in improving prevention and treatment of VAP.

Animal studies showed that macrophage impairment can be restored by antioxidants, and that molecular mechanism of cellular protection could be involved in the physiological response to supra-physiological exposure in ventilated patients (30,31). In an animal study, in which animals were receiving hyperoxemia, ascorbic acid supplementation was associated with significant improvement of *P. Aeruginosa* clearance, and decreased levels of HMGB1, and reactive oxygen species in lung tissue (32).

In addition to the above-discussed limitations, our study was retrospective, and performed in a single center. Therefore, our results could not be generalized to other ICUs. However, the median time spent with hyperoxemia was in line with previous studies. In addition, all VAP episodes were prospectively identified. No data on ventilator settings, Murray score at VAP diagnosis, or on the correlation between PaO_2 and SpO_2 were available. Peripheral vasomotor disorders, low-flow, factors influencing the oxygen dissociation curve (temperature, pH, $PaCO_2$), motion-related artifacts, can alter the measurement of SpO_2 (33). Further, there is heterogeneity in performance of various pulse oximetry devices in ICU, and pulse oximetry could overestimate arterial oxygen saturation. Bias tends to increase with rising lactate and hypoxia (34). However, there is no consensual definition for hyperoxemia in the literature. Further, $SpO_2 \geq 98$ % was used in several recent studies on hyperoxemia (2,12,24-26).

Conclusions

Hyperoxemia at ICU admission, or during ICU stay, had no significant impact on ICU mortality in critically ill patients

with VAP. Further larger multicenter studies are required to better assess the impact of hyperoxemia on mortality in patients with VAP.

Acknowledgements

None.

Footnote

Conflicts of Interest: S Nseir: MSD (lecture), and Ciel Medical (advisory board). This study was presented in part as an abstract at the congress of the French Society of Intensive Care, Paris 2017.

Ethical Statement: The IRB of the Lille University Hospital approved the study and waived informed consent

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