ABENFISIO

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HYPEROXIA AND RESPIRATORY DYSFUNCTION AT ICU ADMISSION ARE ASSOCIATED WITH POOR OUTCOMES IN MECHANICALLY VENTILATED PATIENTS

HIPERÓXIA E DISFUNÇÃO RESPIRATÓRIA ESTÃO ASSOCIADAS COM PIORES DESFECHOS EM PACIENTES SOB VENTILAÇÃO MECÂNICA

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ABSTRACT

Objective: to identify the association of hyperoxia at the time of Intensive Care Unit (ICU) admission with clinical outcomes in adult patients on invasive mechanical ventilation and with respiratory dysfunction defined by a PaO2/FIO2 ratio (P/F) below 300. **Methods**: retrospective cohort observational study with data from adult patients admitted to a general ICU, with 8 beds from a university hospital. Hyperoxia was defined as PaO2 > 120mmHg and patients were classified in 4 subgroups: 1.hyperoxia and P/F > 300, 2. hyperoxia and P/F ≤ 300, 3.no hyperoxia and P/F > 300, and 4. no hyperoxia and P/F ≤ 300. **Results:** a total of 129 patients were included. Hyperoxia was present in one third (43, 33.3%) of all patients. It was more frequent in patients without respiratory dysfunction (P/F ratio > 300, 30 of 54 individuals 55.6%) in comparison to those with respiratory dysfunction (P/F ratio 13 of 88, 14.7%), p=0,044. The ICU mortality was not different among the subgroups; however, the ICU length of stay was greater in the subgroup of patients with hyperoxia and P/F < 300. **Conclusion**: at ICU admission, hyperoxia was more frequent in mechanically ventilated patients without respiratory dysfunction and associated with greater ICU length of stay in those with worse P/F ratio.

Keywords: Hyperoxia; Length of Stay; Prognosis; Respiration, Artificial; Critical Care; Intensive Care Units.

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RESUMO

Objetivo: identificar a associação da hiperóxia no momento da admissão na Unidade de Terapia Intensiva (UTI) com desfechos clínicos em pacientes adultos em ventilação mecânica invasiva e com disfunção respiratória definida pela relação PaO2/FIO2 (P/F) abaixo de 300. **Métodos**: estudo observacional de coorte retrospectivo com dados de pacientes adultos internados em um UTI geral com 8 leitos de um hospital universitário. Hiperóxia foi definida como PaO2 > 120mmHg, e os pacientes foram classificados em 4 subgrupos: 1. hiperóxia e P/F > 300; 2. hiperóxia e P/F ≤ 300; 3. sem hiperóxia e P/F > 300; e 4. não hiperóxia e P/F ≤ 300. **Resultados**: foram incluídos 129 pacientes. A hiperóxia estava presente em um terço (43, 33,3%) de todos os pacientes. Foi mais frequente em pacientes sem disfunção respiratória (relação P/F > 300, 30 de 54 indivíduos 55,6%) em comparação com aqueles com disfunção respiratória (relação P/F 13 de 88, 14,7%), p=0,044. A mortalidade na UTI não foi diferente entre os subgrupos; entretanto, o tempo de permanência na UTI foi maior no subgrupo de pacientes com hiperóxia e P/F < 300. **Conclusão**: na admissão na UTI, a hiperóxia foi mais frequente em pacientes ventilados mecanicamente sem disfunção respiratória e associada a maior tempo de permanência na UTI naqueles com pior relação P/F.

Palavras-chave: Hiperóxia; Duração da estadia; Prognóstico; Respiração Artificial; Cuidados intensivos; Unidades de Terapia Intensiva.

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INTRODUCTION

Tissue hypoxia results in a frequent condition that motivates Intensive Care Unit (ICU) admission, causing impairment of aerobic metabolism, lactic acid generation, and cellular and organ dysfunction[1]. In contrast, hyperoxia, defined by some authors as an arterial oxygen pressure (PaO2) higher than 120mmHg[2,3], has been associated with a bactericidal effect and a decrease in the incidence of operative wound infections[4]. However, the elevation of PaO2 to supraphysiological levels causes greater exposure of lung tissues to Reactive Oxygen Species (ROS), with a consequent increase in pulmonary inflammation, atelectasis, alveolar edema, and adult respiratory distress syndrome[5].

The lung is the first organ involved by the excessive use of O2. Pulmonary capillary endothelial and alveolar epithelial cells are targets for ROS, resulting in injury-induced lung edema, alveolar flooding, hemorrhage, and collagen, elastin, and hyaline membrane deposits[5,6]. Oxygen toxicity caused by ROS progresses in overlapping phases based on the degree of severity and reversibility of injury. However, there are studies that show that even with the improvement of pulmonary exchange, there is a tendency to maintain a high fraction of inspired oxygen (FIO2) in patients undergoing mechanical ventilation (MV)[7,8].

Increased oxidative stress can also have a systemic effect. In an animal model of sepsis, the exposure to hyperoxia was associated with a higher increase in serum ROS and inflammatory cytokines, greater spread of infection, and multiple organ dysfunction. The impairment in microvascular perfusion can induce a paradoxical reduction in regional O2 delivery, although other reports have suggested a beneficial role of hyperoxia in hemodynamic stabilization and redistribution of blood flow to splanchnic organs in animal shock models[9].

Hyperoxia may be present in 1 in 4 critically-ill mechanically ventilated patients. In fact, it is particularly frequent in patients requiring FIO2 less than 50%, as intensivists usually accept higher levels of SpO2 and PaO2 in patients requiring lower FIO2 during invasive MV3. In mechanically ventilated ICU patients, hyperoxia has been associated with a higher mortality rate, a decrease of ventilator free days, an increased rate of nosocomial infections, and worsening of organ dysfunction[10.] The frontier between the therapeutic and deleterious effects of high FIO2 use seems slight. Moreover, the consequences of supra-normal PaO2 exposure in critically ill patients are still unclear[11].

We hypothesize that hyperoxia is frequent in mechanically ventilated patients admitted to the ICU, and it is associated with poor clinical outcomes. This study aims to evaluate the association between PaO2 > 120mmHg and the presence of respiratory dysfunction at the time of ICU admission with clinical outcomes in patients needing invasive MV.

METHODS

This is a retrospective observational cohort study.

Population and design

Data from all patients admitted to the ICU for one year, from March 2017 to March 2018, were evaluated. Inclusion criteria were admission to a clinical general ICU with 8 beds in a university hospital. Patients aged older than 18 years receiving invasive MV at the time of ICU admission were included. Patients under noninvasive ventilation (NIV), with an ICU length of stay less than 3 days or under palliative care were excluded from the study.

Data collection and variables

The data used for the analysis were recorded in a database routinely used for documentation and patient care from the day of admission to the ICU, and throughout the stay in the unit.

Demographic variables (age and sex), Acute Physiology and Chronic Health Evaluation II severity score (APACHE II)[12], and Sequential Organ Failure Assessment score (SOFA)[13] at ICU admission were collected from the database.

Arterial blood gases were collected in the first 24 hours after ICU admission. The FIO2 at the time arterial blood gases analysis was recorded and the PaO2/FIO2 ratio (P/F) was calculated.

We defined hyperoxia as PaO2 greater than or equal to 120mmHg[14-17], measured at the moment of ICU admission. Patients were divided in four subgroups, according to the presence of hyperoxia and respiratory dysfunction at ICU admission. Subgroup 1: Hyperoxia without respiratory dysfunction (PaO2 > 120mmHg and P/F ratio > 300); Subgroup 2: Hyperoxia with respiratory dysfunction (PaO2 > 120mmHg and P/F ratio < 300); Subgroup 3: No hyperoxia without respiratory dysfunction (PaO2 < 120mmHg and P/F ratio > 300); and Subgroup 4: No hyperoxia with respiratory dysfunction (PaO2 < 120mmHg and P/F ratio < 300).

We assessed the frequency of hyperoxia according to the presence or absence of respiratory dysfunction and the following clinical outcomes: new organic dysfunctions (neurological, cardiologic, hepatic, renal, and hematologic) on the third day of hospitalization in the ICU, need for tracheostomy, MV need at the time of discharge, ICUs length of stay, and mortality.

Statistical Analysis

Data were subjected to descriptive statistical analyses of univariate nature for continuous variables (measures of central tendency and dispersion) and categorical (relative frequencies). For bivariate analyses, Chi-square test and Fisher's exact test were used for the analysis of categorical variables, while ANOVA and Kruskal-Wallis test were used to compare continuous variables with normal and non-normal distribution, respectively. A generalized linear model was performed to assess whether the relationship between ICU length of stay and hyperoxia was independent of patient severity by the Wald chi-squared test. The p-value ≤ 0.05 was adopted as an index of significance

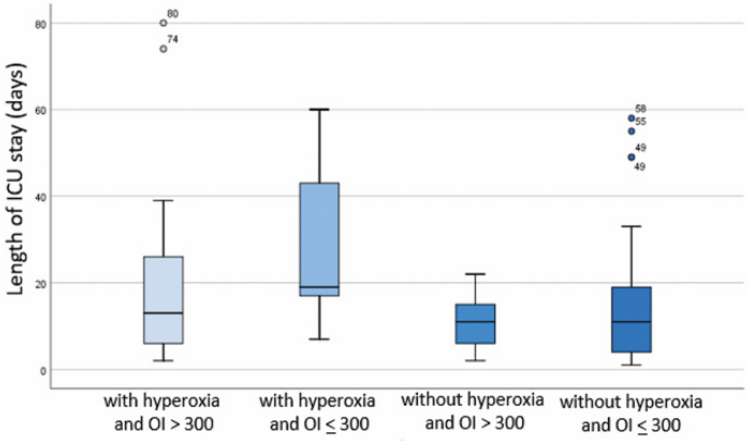
Ethics

The study was approved by the institutional Research Ethics Committee (CAAE: 64529817.1.0000.5045). Because it is a retrospective study with the collection of data recorded in a unit database, the completion of the Informed Consent Form was waived. The study followed the 466/12 resolution of the National Health Council and the Helsinki Declaration.

RESULTS

A total of 186 patients were admitted to the ICU during the study period, of which 132 required the use of invasive MV. A total of 3 patients were excluded because they had a length of ICU stay of less than 12 hours. The remaining 129 patients were divided into the 4 subgroups according to the occurrence of hyperoxia and respiratory dysfunction (Figure 1).

Figure 1. Length of ICU stay in subgroup of patients with and without hyperoxia and with and without oxygenation impairment



Source: prepared by the authors.
Note: P/F: PaO2/FIO2; One-Way ANOVA (Kruskal-Wallis), p-value: 0.006.

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Different clinical conditions at ICU admission determined a heterogeneous sample. Circulatory shock was identified in 47 patients (36.4%); sepsis in 97 patients (75.2%); respiratory failure in 65 (50.4%); and altered level of consciousness in 60 patients (46.5%).

Hyperoxia was present in one third (43, 33.3%) of all patients. It was more frequent in patients without respiratory dysfunction (30 of 54, 55.6%) in comparison to those with lower P/F ratio (13 of 88, 14.7%), p=0,044.

The mean age of the patients was 57.8 ± 17.3 years-old and the majority was female (60.5%). At admission to the ICU, the mean APACHE II score was 20.4 ± 6.6 points and the SOFA score was 8.2 ± 4.3 points.

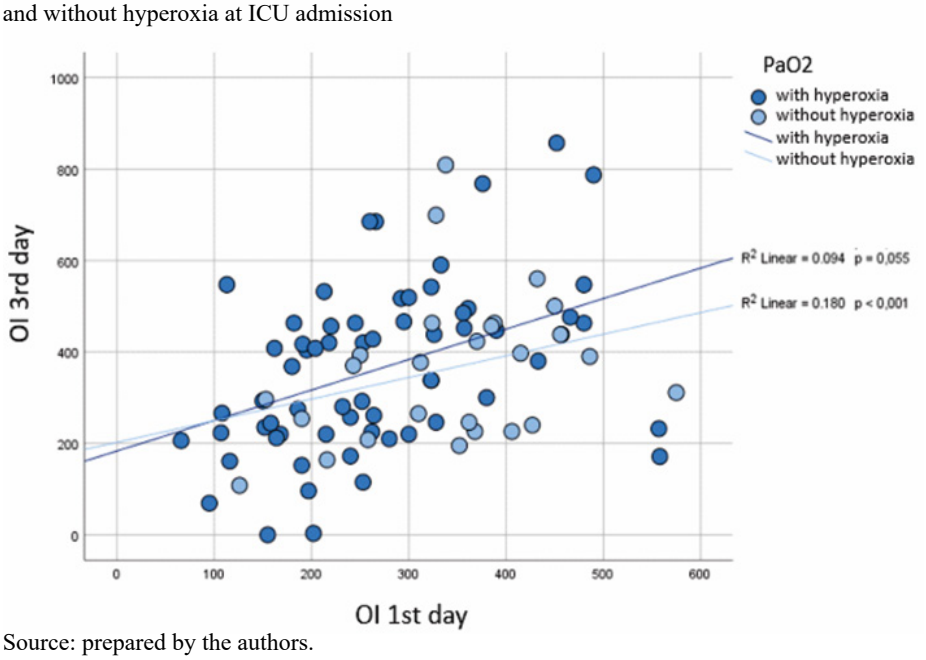
There was no statistical difference between the subgroups concerning age, sex, APACHE II score, and SOFA score. Regarding outcomes, ICU mortality was similar between the subgroups, however, patients with hyperoxia and respiratory dysfunction at ICU admission remained longer in the unit (Table 1 and Figure 2).

Table 1. Comparison among the subgroups of patients admitted to the ICU with and without hyperoxia (N=129)

Variables	**Hyperoxia** (PaO_2>120mmHg)		**No hyperoxia** (PaO_2≤120mmHg)		**p-value**
	P/F > 300 (N=30)	P/F ≤ 300 (n=13)	P/F > 300 (N=24)	P/F ≤ 300 (N=62)	
Age, (years)*	56 ± 17	62 ± 14	54 ± 15	58 ± 19	0.284[f]
Female, (%)	56.7	53.8	25	37.1	0.077[c]
APACHE II score*	19.9 ± 6.7	20.2 ± 7.3	19.2 ± 4.9	21.1 ± 7.2	0.597[e]
SOFA (1st day)**	7 (4-9)	7 (5–9.5)	7 (4-11)	8.5 (5-12)	0.249[f]
Outcomes in the ICU					
New organ disf., (%)					
Neurological	26.1	50.0	56.5	34.0	0.059[d]
Cardiovascular	34.8	66.7	60.9	46.3	0.055 [d]
Hepatic	18.2	20.0	27.8	18.2	0.079 [d]
Renal	41.7	28.6	39.1	18.5	0.034 [d]
Hematologic	33.3	57.1	21.7	25.9	0.042 [d]
Tracheostomy, (%)	55.0	100	39.1	100	0.039 [d]
MV at discharge, (%)	11.1	0	5.0	10.4	0.713 [d]
Length of stay (days)**	13 (6–26)	19 (17–43)	11(6–15)	11 (4–19)	0.006[d]
Death, (%)	46.7	53.9	54.2	61.3	0.608[d]

Source: prepared by the authors.
Note: * Mean ± standard deviation ** Median (25% and 75% percentiles). P/F: PaO2/FIO2; SOFA: Sequential Organ Failure Assessment; MV: mechanical ventilation; c: Pearson's Qui-Square test; d: Fisher's exact test; e: ANOVA; f: Kruskal-Wallis test.

Figure 2. Correlation between oxygenation index on the first and third day in the subgroups of patients with and without hyperoxia at ICU admission



Source: prepared by the authors.
Note: P/F: PaO2/FIO2 ratio; R²: Spearman's correlation coefficient.

The ICU length of stay remained longer in patients with hyperoxia with respiratory dysfunction regardless of patients' severity of illness as assessed by fixing the APACHE II score in 22.4 for all groups (Table 2).

Table 2. Comparison of mean ICU length of stay with APACHE II score fixed in the value 20.4 (N=129)

			95% CI of Wald	
	Mean	SD*	Low	High
PaO_2 >120mmHg and P/F > 300	19.5	3.0	14.3	26.5
PaO_2 >120mmHg and P/F ≤ 300	26.7	6.2	16.9	42.8
PaO_2 ≤120mmHg and P/F > 300	10.9	1.9	7.7	15.4
PaO_2 ≤120mmHg and P/F ≤ 300	13.6	1.4	11.0	16.8

Source: prepared by the authors.
Note: * SD: standard deviation; P/F: PaO2/FIO2 ratio. Wald chi-square test (χ^2: 10.092; p-value: 0.018).

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DISCUSSION

The main findings of the present investigation were the following: unplanned exposure to hyperoxia was more frequent in patients admitted with respiratory dysfunction and is associated with increased ICU length of stay in patients who had both hyperoxia and P/F ratio below 300. Hyperoxia was related to an increase in ICU length of stay, regardless of the severity of the patients, calculated by the APACHE II score.

An elevation of oxygen partial pressure increases the amount of ROS, generates an inflammatory component, and causes extensive cellular damage[18-20]. Previous studies have shown that an FIO2 > 0.6 for 48 hours or more seems to induce lung injury mechanical with an inflammatory component similar to that found in Adult Respiratory Distress Syndrome, increasing morbidity and mortality, hospitalization time, and costs[21-24].

Some authors failed to relate hyperoxia to in-hospital mortality. However, these results were interpreted as influenced by the method applied in the investigation[25,26]. Meanwhile, other studies have found that longer exposures to hyperoxia is associated with an increased risk for unfavorable outcomes, such as on mortality and subsequent organ dysfunction[27,28].

In 2016, the World Health Organization (WHO) strongly recommended the use of a high FIO2 in adult patients undergoing general anesthesia to reduce the risk of surgical site infection[4]. Although this exposure to hyperoxia for a short period may be beneficial in surgical patients[27,28], there is no evidence to support the extension of this recommendation to critically ill patients, especially those with pulmonary compromise.

Previous studies have shown an association between increased mortality and hyperoxia in patients with traumatic brain injury, cardiac arrest, and cerebrovascular events[11,29]. In this study, the association between ICU mortality and hyperoxia at admission was not identified. One possible explanation is the heterogeneity of diseases and the low number of patients evaluated.

In the same way as this study, others authors have identified the relationship between hyperoxia and organic dysfunctions, including respiratory dysfunction[24,25]. However, these are observational studies and point to the need for randomized clinical trials.

This study has limitations. It was carried out in a single-center university and tertiary hospital, a reference unit for the regional public health system. It assists patients with complex diseases with multiple comorbidities. In addition, as this was a retrospective study, other data on MV, which could further clarify the size of the impact of hyperoxia in the prognosis of patients, were not analyzed.

Despite these limitations, the present investigation was able to show the more frequency of hyperoxia in patients without respiratory dysfunction and its association with an increase in the length of ICU stay and worsening of gas exchange in patients admitted with respiratory dysfunction assessed by the P/F ratio. This data is of clinical relevance, since it is an alert to the benefit of greater vigilance to avoid hyperoxia in all patients, but with more attention to those admitted with respiratory dysfunction. Future clinical trials should address strategies to decrease the prevalence of hyperoxia in mechanically ventilated patients with respiratory compromise and to assess its impacts on relevant clinical outcomes.

In conclusion, inadvertent hyperoxia at ICU admission is more frequent in patients without respiratory dysfunction and associated with greater ICU length of stay regardless of the clinical severity of the patient. This study warns about the need for rational use of supplemental oxygen in critically ill patients. It also points to the need for multicenter, prospective, and randomized studies to evaluate the benefits of careful titration of FIO2 to avoid hyperoxia during invasive ventilatory support.

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