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ORIGINAL ARTICLE

Impacts of a fraction of inspired oxygen adjustment protocol in COVID-19 patients under mechanical ventilation: A prospective cohort study

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KEYWORDS
COVID-19;
Hyperoxia;
Intensive care unit;
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Abstract
Objective: We examined weather a protocol for fraction of inspired oxygen (FiO_2) adjustment can reduce hyperoxemia and excess oxygen use in COVID-19 patients mechanically ventilated.
Design: Prospective cohort study.
Setting: Two intensive care units (ICUs) dedicated to COVID-19 patients in Brazil.
Patients: Consecutive patients with COVID-19 mechanically ventilated.
Interventions: One ICU followed a FiO_2 adjustment protocol based on SpO_2 (conservative-oxygen ICU) and the other, which did not follow the protocol, constituted the control ICU.
Main variables of interest: Prevalence of hyperoxemia (PaO_2 >100 mmHg) on day 1, sustained hyperoxemia (present on days 1 and 2), and excess oxygen use (FiO_2 > 0.6 in patients with hyperoxemia) were compared between the two ICUs.
Results: Eighty two patients from the conservative-oxygen ICU and 145 from the control ICU were included. The conservative-oxygen ICU presented lower prevalence of hyperoxemia on day 1 (40.2% vs. 75.9%, $p < 0.001$) and of sustained hyperoxemia (12.2% vs. 49.6%, $p < 0.001$). Excess oxygen use was less frequent in the conservative-oxygen ICU on day 1 (18.3% vs. 52.4%, $p < 0.001$). Being admitted in the control ICU was independently associated with hyperoxemia and excess oxygen use. Multivariable analyses found no independent relationship between day 1 hyperoxemia, sustained hyperoxemia, or excess FiO_2 use and adverse clinical outcomes.
Conclusions: Following FiO_2 protocol was associated with lower hyperoxemia and less excess oxygen use. Although those results were not associated with better clinical outcomes, adopting FiO_2 protocol may be useful in a scenario of depleted oxygen resources, as was seen during the COVID-19 pandemic.

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PALABRAS CLAVE
COVID-19;
Hiperoxemia;
Unidades de cuidados intensivos;
Ventilación mecánica

Impactos de un protocolo de ajuste de la fracción de oxígeno inspirado en pacientes con COVID-19 sometidos a ventilación mecánica: un estudio de cohorte prospectivo

Resumen
Objetivo: Evaluar si un protocolo para el ajuste de la FiO_2 reduce la hiperoxemia y el uso excesivo de oxígeno en pacientes con COVID-19 en ventilación mecánica.
Diseño: Estudio de cohorte prospectivo.
Ámbito: Unidades de cuidados intensivos (UCI) dedicadas a pacientes con COVID-19 en Brasil.
Pacientes: Pacientes con COVID-19.
Intervenciones: Una UCI siguió un protocolo de ajuste de FiO_2 basado en SpO_2 (UCI de oxigenoterapia conservadora, N = 82) y la otra no siguió el protocolo (UCI control, N = 145).
Principales variables de interés: Prevalencia de hiperoxemia (PaO_2 > 100 mmHg) en el día 1, hiperoxemia sostenida (presente en los días 1 y 2) y exceso de uso de oxígeno (FiO_2 > 0,6 en pacientes con hiperoxemia) entre las 2 UCI.
Resultados: La UCI de oxigenoterapia conservadora presentó menor prevalencia de hiperoxemia en el día 1 (40,2 vs. 75,9%; p < 0,001) y de hiperoxemia sostenida (12,2 vs. 49,6%; p < 0,001). El uso excesivo de oxígeno fue menos frecuente en la UCI de oxigenoterapia conservadora el día 1 (18,3 vs. 52,4%; p < 0,001). El ingreso en la UCI control se asoció de forma independiente con la hiperoxemia y el uso excesivo de oxígeno. Los análisis multivariables no encontraron una relación independiente entre hiperoxemia o uso excesivo de FiO_2 y resultados clínicos adversos.
Conclusiones: Seguir el protocolo de FiO_2 se asoció con menor hiperoxemia y menor consumo de oxígeno en exceso. Aunque esos resultados no se asociaron con mejores resultados clínicos, la adopción del protocolo FiO_2 puede ser útil en un escenario de recursos de oxígeno agotados, como se vio durante la pandemia de COVID-19.

Introduction

Patients with severe COVID-19 pneumonia may require invasive mechanical ventilation (MV) due to acute respiratory distress syndrome (ARDS). MV is highly effective in increasing oxygenation and reverting hypoxemia, even in patients with severe forms of ARDS.[1,2] However, during MV, patients are frequently exposed to high fractions of inspired oxygen (FiO_2), sometimes higher than necessary.[3,4] This exposure to high FiO_2 can induce pulmonary inflammation due to excessive production of reactive oxygen species, as demonstrated by experimental studies.[5,6] Another possible consequence of ventilating patients with high FiO_2 is the occurrence of hyperoxemia, defined by arterial partial pressure of oxygen (PaO_2) higher than 100 mmHg.[7] Hyperoxemia has been associated with worse outcomes in critically ill patients with acute brain or myocardial injury, and patients resuscitated post cardiac arrest, possible due to vasoconstriction in the cerebral and coronary circulation.[8]

However, the impact of hyperoxemia in mechanically ventilated patients due to ARDS is still controversial. The LUNG SAFE study showed that, among 2005 ARDS patients, 30% had hyperoxemia on the first day of MV and 12% had hyperoxemia on both the first and second days of MV. Despite its frequency, hyperoxemia was not associated with higher mortality in this observational study.[7] Two recent randomized clinical trials compared a conservative oxygen therapy (targeting a PaO_2 between 55 and 70 mmHg) with a liberal oxygen therapy (targeting a PaO_2 between 90 and 105 mmHg), in patients with ARDS.[9,10] Those studies did not show significant differences between the two groups in mortality, length of intensive care unit (ICU) stay or duration of MV. Those results showed that a more conservative oxygen use is safe and can reduce costs and spare oxygen, a gas that became scarce in some regions during the COVID-19 pandemic.[11]

During the COVID-19 pandemic, several ICUs were overburdened and had to treat a high number of patients, several times with insufficient expert staff and lack of equipment. The overload ICUs and the overwhelmed staffs might have reduced the compliance with the best practices in MV and were associated with excess mortality.[12] Therefore, our hypotheses are: 1. hyperoxemia and excess oxygen use are frequent among COVID-19 patients under MV; 2. following a structured protocol to reduce FiO_2 based on the peripheral oxygen saturation (SpO_2) reduces the occurrence of hyperoxemia and excess oxygen use. To investigate those hypotheses, we compared two cohorts of COVID-19 patients, one conducted in an ICU with a protocol to adjust the FiO_2 systematically and the other without a protocol to adjust the FiO_2.

Patients and methods

This is a prospective cohort study conducted in two ICUs dedicated to COVID-19 patients in two public hospitals in Juiz de Fora (Minas Gerais, Brazil): Federal University of Juiz de Fora University Hospital and Regional Doutor João Penido Hospital. Patients were included from March, 2020 to June, 2021. The study protocol followed the ethical principles of the

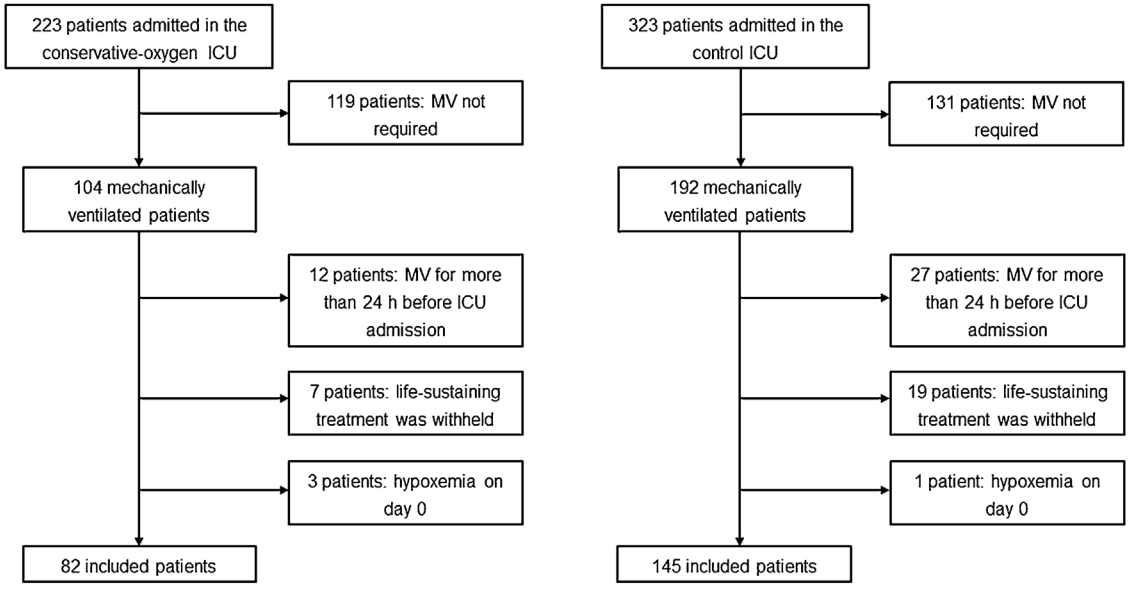

Figure 1 Study participant flow chart. Flow of potentially eligible participants in the study, and final numbers included and analyzed in each cohort.

Declaration of Helsinki and was approved by the Ethics Committees of both hospitals and written informed consent was obtained from the patients' next of kin (protocol number 3.949.165).

Patients

Consecutive patients aged 18 years or older, admitted to one of the two participating ICUs with COVID-19 confirmed by RT-PCR, and who received invasive MV were eligible for participating in the study. We excluded patients who had received invasive MV for more than 24 h before admission in the participating ICUs, patients who were ventilated for less than 48 h, and those for whom life-sustaining treatment was withheld. Since the study focus was on hyperoxemia and excess oxygen use, we excluded patients with hypoxemia (PaO_2 < 55 mmHg, regardless of the FiO_2) on day 0, defined as the calendar day when the patient was intubated.

FiO_2 adjustment protocol

A FiO_2 adjustment protocol was already applied in one of the participant ICUs. The same protocol was also applied in the ICU dedicated to COVID-19 patients in this hospital (conservative-oxygen ICU). According to this protocol, patients under MV and with positive end-expiratory pressure (PEEP) equal or lower than 8 cmH_2O were evaluated every 1 h by a nurse, who adjusted FiO_2 based on SpO_2. If SpO_2 was higher than 96%, FiO_2 was reduced in 10% (absolute value); if SpO_2 was between 93% and 96%, FiO_2 was maintained; and if SpO_2 was lower than 93%, the doctor in charge was called. In patients with PEEP higher than 8 cmH_2O, the nurses did not adjust FiO_2, but they called the doctor in charge if SpO_2 was lower than 93% (eFigure 1 in Supplementary Appendix). In the other hospital, the ICU dedicated to COVID-19 patients did not adopt any FiO_2 protocol and constituted the control-ICU.

The other ventilatory parameters were set by the doctors in charge, who were orientated to keep a protective MV (Appendix A). Neither inhaled nitric oxide (NO), nor extracorporeal membrane oxygenation (ECMO) were available in the ICUs.

Data collection

At ICU admission, the following patient's characteristics were prospectively recorded: age, sex, body-mass index (BMI), Charlson Comorbidity Index, Simplified Acute Physiology Score (SAPS-III), Sequential Organ Failure Assessment (SOFA), and laboratory tests.

The following ventilatory parameters were collected on day 1 and day 2, as close as possible to 8 a.m. each day: tidal volume (V_T), respiratory rate, FiO_2, PEEP, plateau pressure, driving pressure (plateau pressure minus total PEEP), respiratory system compliance (V_T divided by driving pressure). Arterial blood gas analysis was recorded simultaneously with the ventilatory parameters. For each day until ICU discharge or death, assessment was made as to whether patients were under MV or not. Patient survival was evaluated at day 90.

Outcomes

The primary outcomes were the prevalence of hyperoxemia and excess oxygen use on day 1 and day 2 in both cohorts. We defined hyperoxemia as PaO_2 > 100 mmHg and excess oxygen use as FiO_2 > 0.6 in patients with hyperoxemia. Sustained hyperoxemia was defined as the presence of hyperoxemia on days 1 and 2.

Secondary outcomes included: occurrence of hypoxemia (defined as PaO_2 < 55 mmHg, regardless of FiO_2), number of ventilator-free days at day 28, length of stay in the

Table 1 Characteristics of the patients on day 1.

	Conservative-oxygen ICU	Control ICU	*p*-Value
Age (years), median (IQR)	61 (47–70)	65 (55–75)	0.02
Male, n (%)	44 (53.7)	77 (53.1)	0.93
SAPS III, median (IQR)[a]	43 (39–52)	46 (41–54)	0.14
SOFA score, median (IQR)	7 (5–8)	6 (3–7)	<0.0001
Non-respiratory SOFA, median (IQR)	4 (3–5)	3 (1–5)	0.06
Charlson index, median (IQR)	2 (1–4)	3 (2–5)	<0.001
PaO_2/FiO_2, median (IQR)	189 (164–241)	204 (145–260)	0.87
ARDS severity, n (%)[a]			
Mild	22 (29.7)	29 (21.2)	0.26
Moderate	41 (55.4)	78 (56.9)	
Severe	11 (14.9)	30 (21.9)	
$PaCO_2$ (mmHg), median (IQR)	47 (40–54)	45 (39–52)	0.27
Arterial pH, median (IQR)	7.33 (7.28–7.39)	7.34 (7.27–7.41)	0.87
Bicarbonate (mmol/L), median (IQR)	25 (22–29)	23 (21–27)	0.02
C-reactive protein (mg/L), median (IQR)	184 (85–275)	142 (81–194)	<0.001
FiO_2, median (IQR)	0.5 (0.4–0.6)	0.6 (0.5–0.8)	<0.0001
$FiO_2 \geq 0.6$, n (%)	16 (19.5)	72 (49.7)	<0.0001
Respiratory rate (breaths/min), median (IQR)	25 (22–28)	24 (20–26)	<0.001
Tidal volume (mL/kg PBW), median (IQR)	6.5 (6.1–7.1)	6.4 (5.9–7.4)	0.58
Plateau pressure (cmH_2O), median (IQR)	22 (20–25)	25 (22–28)	<0.0001
Driving pressure (cmH_2O), median (IQR)	12 (10–14)	14 (12–16)	<0.001
PEEP (cmH_2O), median (IQR)	10 (8–12)	12 (10–12)	<0.001
C_{RS} (mL/cmH_2O), median (IQR)	33 (26–39)	29 (24–35)	0.03

Abbreviations: ARDS, acute respiratory distress syndrome; C_{RS}, respiratory system compliance; FiO_2, fraction of inspired oxygen; IQR, interquartile range; PaO_2, arterial oxygen partial pressure; $PaCO_2$, arterial carbon dioxide partial pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SAPSIII, simplified acute physiology score; SOFA, Sequential Organ Failure Assessment.
[a] SAPS III and ARDS severity were collected at admission in the ICU.

ICU, ICU mortality, hospital mortality, and 90-day mortality. Ventilator-free days were defined as calendar days of unassisted breathing for at least 24 consecutive hours. In patients who died by day 28, ventilator-free days were considered 0.

Statistical analysis

A convenience sample was considered for this study, and consecutive patients were included. No assumptions were made for missing data. Categorical variables were expressed as absolute numbers and percentages and continuous variables, as medians and interquartile ranges. For categorical variables, the two cohorts were compared by the chi-square test; for continuous variables, they were compared by the Wilcoxon rank-sum test.

Multivariable logistic regression models considering the ICU admission (conservative-oxygen or control ICU) as the predictor of interest was constructed to assess variables independently associated with hyperoxemia and with excess oxygen use. The following variables were selected for initial assessment according to clinical relevance: age, gender, Charlson comorbidity index, SAPS-III, non-respiratory SOFA on day 1, laboratory tests at admission (D-dimer, C-reactive protein, ferritin, and lactic dehydrogenase), respiratory parameters on day 1 (respiratory system compliance, plateau pressure, driving pressure, PEEP, V_T, PaO_2/FiO_2, $PaCO_2$, pH, bicarbonate). Variables with a $p < 0.20$ in the univariable prediction model were included in the multivariable model. Results were reported as odds ratio (OR) with 95% confidence interval (CI).

Another multivariable logistic regression model considering hyperoxemia on day 1, sustained hyperoxemia or excess oxygen use as the predictor of interest was constructed to assess variables independently associated with hospital mortality. The same variables selected above were initially assessed and those with a $p < 0.20$ in the univariable prediction model were included in the multivariable model. Results were reported as OR with 95% CI.

All statistics tests were two-tailed with a significance level of 0.05. Data were analyzed with Stata 15.1 (StataCorp LP, College Station, TX, USA).

Results

During the enrollment period, 82 from the conservative-oxygen ICU and 145 from the control ICU (Fig. 1). Table 1 shows demographic, clinical characteristics, and the ventilator settings on day 1 of MV from patients in the two participating ICUs.

Patients from the conservative-oxygen ICU, compared with those from the control ICU, presented lower PaO_2 and lower FiO_2 on day 1 and day 2 of MV (Table 2). The PaO_2 was lower in the conservative-oxygen ICU group in all different levels of FiO_2 uses, on days 1 and 2 (Fig. 2a and b). The proportions of patients with hyperoxemia on day 1 and with sustained hyperoxemia were lower in

Table 2 Occurrence of hyperoxia, excess oxygen use and clinical outcomes in the two groups.

	Conservative-oxygen ICU	Control ICU	*p*-Value
PaO_2 at day 1 (mmHg), median (IQR)	92 (81–112)	125 (101–160)	<0.0001
PaO_2 at day 2 (mmHg), median (IQR)	91 (78–106)	121 (90–146)	<0.0001
Hyperoxemia at day 1, n (%)	33 (40.2)	110 (75.9)	<0.0001
Hyperoxemia at day 2, n (%)	27 (32.9)	95 (65.5)	<0.0001
Sustained hyperoxemia, n (%)	10 (12.2)	72 (49.6)	<0.0001
Hypoxemia at day 1, n (%)	0 (0)	0 (0)	1
Hypoxemia at day 2, n (%)	0 (0)	0 (0)	1
FiO_2 at day 1, median (IQR)	0.50 (0.40–0.60)	0.60 (0.50–0.80)	<0.0001
FiO_2 at day 2, median (IQR)	0.47 (0.40–0.55)	0.55 (0.50–0.70)	<0.0001
Excess oxygen use at day 1, n (%)	15 (18.3)	76 (52.4)	<0.0001
Excess oxygen use at day 2, n (%)	9 (10.9)	51 (35.2)	<0.0001
Ventilator free days (days), median (IQR)			
All	0 (0–19)	0 (0–16)	0.46
Survivors at ICU discharge	18 (7–22)	16 (5–21)	0.31
ICU length of stay (days), median (IQR)			
All	16 (7–31)	16 (9–27)	0.91
Survivors at ICU discharge	18 (11–33)	16 (10–28)	0.42
28-day mortality	30 (36.6)	55 (37.9)	0.84
60-day mortality	34 (41.6)	74 (51.3)	0.17
Hospital mortality	40 (48.8)	78 (53.8)	0.46

Abbreviations: FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; PaO_2, arterial oxygen partial pressure.

the conservative-oxygen ICU (Table 2), a result that was consistent in all different levels of FiO_2 uses (Fig. 2c and d). Density distributions of PaO_2 on days 1 and 2 reveal different profiles between the two ICUs (Fig. 2e and f). Excess oxygen use was less frequent in the conservative-oxygen ICU on day 1 (18.3% versus 52.4%, $p < 0.001$), and day 2 (10.9% versus 35.2%, $p < 0.001$) (Table 2). No patients from both ICUs had hypoxemia on days 1 and 2 (Table 2).

Multivariable analyses identified that being admitted in the control ICU and higher PaO_2/FiO_2 as factors independently associated with hyperoxemia on day 1, and being admitted in the control ICU, higher PaO_2/FiO_2, and lower protein C-reactive levels as factors independently associated with sustained hyperoxemia (Table 3). The independently factors associated with excess oxygen use on day 1 were being admitted in the control ICU and lower compliance of the respiratory system (Table 3).

Ventilator free days, length of stay in the ICU, 28-day mortality, 90-day mortality, and hospital mortality did not differ significantly between the two groups. Hyperoxemia on day 1, sustained hyperoxemia and excess oxygen use on day 1 were not independently associated with hospital mortality (Table 4).

Discussion

This study showed that following a structured protocol to reduce FiO_2 based on SpO_2 was associated with reduction of hyperoxemia on day 1 and sustained hyperoxemia. Moreover, excess oxygen use was lower in the conservative-oxygen ICU compared with control ICU, and this reduction was not associate with hypoxemia occurrence. We found no relationship between hyperoxemia or excess oxygen use and hospital mortality in our cohort of COVID-19 under mechanical ventilation.

Other studies have demonstrated that hyperoxemia occurs in mechanically ventilated patients and that higher FiO_2 than necessary is set in these patients. A retrospective study that evaluated patients under MV showed that 49.8% presented hyperoxemia during the first 24 h of MV, among whom the mean FiO_2 was 62%.[13] The LUNG SAFE study, a prospective cohort of patients with ARDS under MV, showed that 30% of them presented hyperoxemia on day 1 of MV, and 12% sustained hyperoxemia on days 1 and 2 of MV. Among patients with hyperoxemia, 66% were ventilated with FiO_2 higher than 60%.[7]

The multivariable analysis also showed that being admitted in the conservative-oxygen ICU was associated with lower occurrence of hyperoxemia. This result suggests that following a structured protocol of FiO_2 adjustment reduces oxygen use and the occurrence of hyperoxemia, without increasing the risk of hypoxemia, which was not observed in any of the patients in the two ICUs on days 1 and 2. A possible reason for the excessive use of oxygen and the high number of hyperoxemic patients during MV might be that doctors are more worried about hypoxemia than hyperoxemia. Therefore, FiO_2 reduction tends to be avoided. Other factors might have contributed to the excess use of oxygen, especially during the COVID-19 pandemic. The massive number of patients mechanically ventilated in the ICUs during the pandemic resulted in work overload for the health care professionals. This fact may have reduced the frequency in which the ventilatory parameters were adjusted. Moreover, less specialized staff worked in the ICUs during the pandemic, with

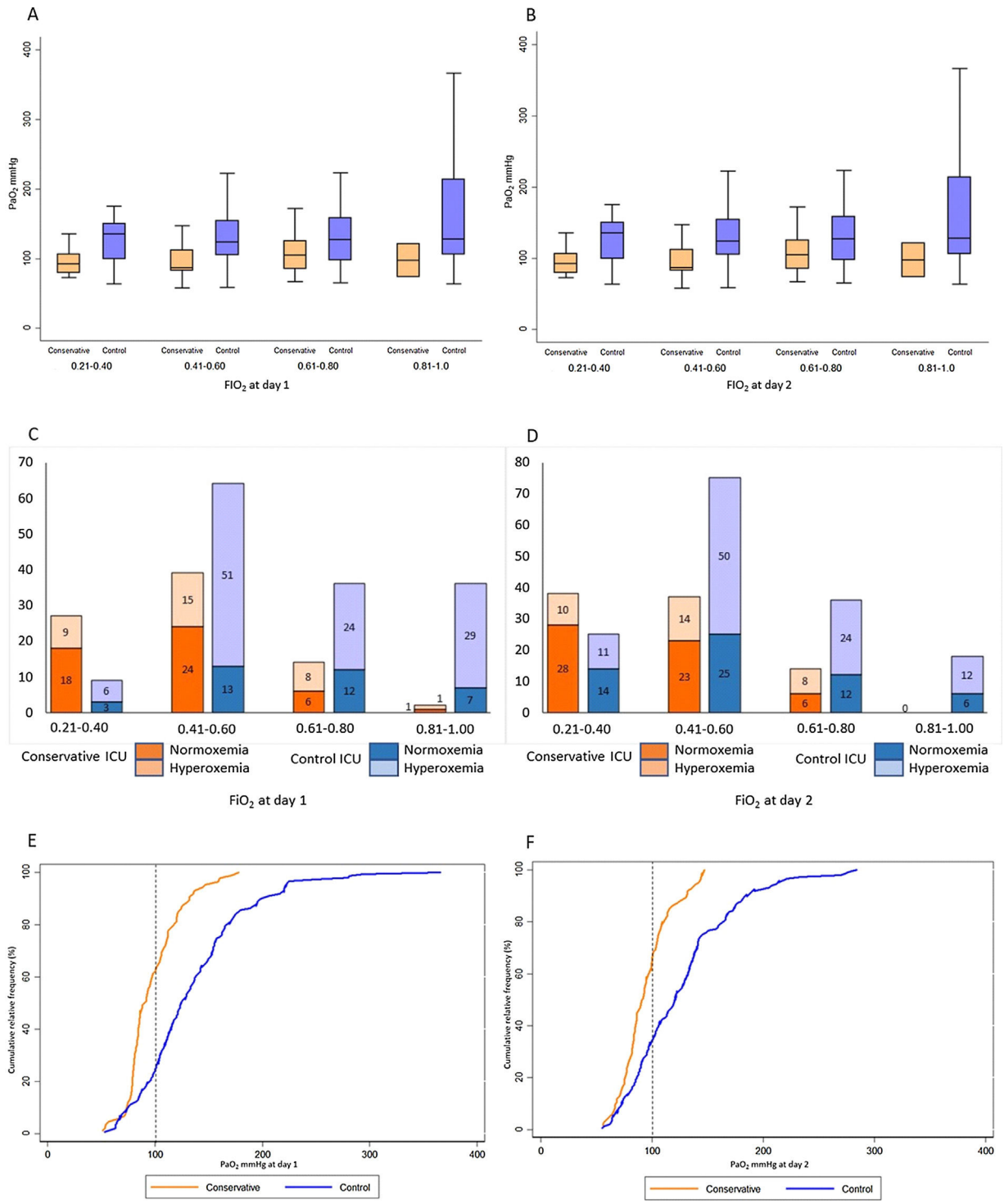

Figure 2 Arterial oxygen tension and use of oxygen on days 1 and 2 of mechanical ventilation. A. Box plot of PaO_2 at different ranges of FiO_2 in the conservative-oxygen and control ICUs on day 1. B. Box plot of PaO_2 at different ranges of FiO_2 in the conservative-oxygen and control ICUs on day 2. C. Frequency of patients with hyperoxemia and normoxemia at different ranges of FiO_2 in the conservative-oxygen and control ICUs on day 1. D. Frequency of patients with hyperoxemia and normoxemia at different ranges of FiO_2 in the conservative-oxygen and control ICUs on day 2. E. Density distributions of PaO_2 in the conservative-oxygen and control ICUs on day 1. F. Density distributions of PaO_2 in the conservative-oxygen and control ICUs on day 2.

Table 3 Factors associated with day 1 hyperoxemia, sustained hyperoxemia and excess oxygen use.

	Odds ratio (95% confidence interval)	*p*-Value
Outcome – hyperoxemia at day 1		
Being admitted to control ICU	9.04 (3.94–20.73)	<0.0001
Non-respiratory SOFA	1.00 (0.87–1.16)	0.99
C-reactive protein admission (mg/L)	1.00 (0.99–1.00)	0.89
PaO_2/FiO_2 at day 1	1.02 (1.02–1.03)	<0.0001
Bicarbonate (mmol/L)	0.96 (0.90–1.03)	0.21
Driving pressure (cmH_2O)	1.08 (0.97–1.21)	0.18
Outcome – sustained hyperoxemia (day 1 and 2)		
Being admitted to control ICU	6.73 (2.98–15.19)	<0.0001
Non-respiratory SOFA score	1.04 (0.92–1.18)	0.53
C-reactive protein admission (mg/L)	0.99 (0.99–1.00)	0.04
PaO_2/FiO_2 at day 1	1.01 (1.01–1.01)	<0.0001
Bicarbonate (mmol/L)	0.99 (0.93–1.05)	0.67
Driving pressure (cmH_2O)	1.06 (0.96–1.17)	0.23
Outcome – excess oxygen use at day 1		
Being admitted to control ICU	4.85 (2.44–9.61)	<0.0001
PEEP (cmH_2O)	1.18 (0.99–1.41)	0.06
Plateau pressure (cmH_2O)	0.94 (0.83–1.06)	0.29
C_{RS} (mL/cmH_2O)	0.95 (0.91–0.99)	0.02

Abbreviations: C_{RS}, respiratory system compliance; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; PaO_2, arterial oxygen partial pressure; PEEP, positive end-expiratory pressure; SOFA, Sequential Organ Failure Assessment.

Table 4 Factors associated with hospital mortality in study population.

Factor	Odds ratio (95% CI), *p* Hyperoxemia on day 1 as the predictor of interest	Odds ratio (95% CI), *p* Sustained hyperoxemia as the predictor of interest	Odds ratio (95% CI), *p* Excess oxygen use on day 1 as the predictor of interest
Hyperoxemia on day 1	1.07 (0.48–2.39), $p = 0.86$		
Sustained hyperoxemia		1.01 (0.47–2.14), $p = 0.98$	
Excess oxygen use on day 1			1.10 (0.54–2.24), $p = 0.80$
Age	1.08 (1.04–1.11), $p < 0.0001$	1.08 (1.04–1.11), $p < 0.0001$	1.08 (1.04–1.11), $p < 0.0001$
SOFA score day 1	1.29 (1.10–1.52), $p = 0.002$	1.29 (1.10–1.52), $p = 0.002$	1.29 (1.10–1.52), $p = 0.002$
Lactic dehydrogenase (IU/L)	1.00 (0.99–1.00), $p = 0.33$	1.00 (0.99–1.00), $p = 0.35$	1.00 (0.99–1.00), $p = 0.33$
Driving pressure (cmH_2O)	1.13 (1.02–1.26), $p = 0.02$	1.14 (1.02–1.27), $p = 0.02$	1.13 (1.02–1.26), $p = 0.02$
Bicarbonate (mmol/L)	1.04 (0.97–1.10), $p = 0.28$	1.04 (0.97–1.10), $p = 0.29$	1.04 (0.97–1.11), $p = 0.28$
PaO_2/FiO_2 at day 1	0.99 (0.99–1.00), $p = 0.58$	0.99 (0.99–1.00), $p = 0.60$	0.99 (0.99–1.00), $p = 0.60$
Renal replacement therapy	2.38 (1.02–5.54), $p = 0.04$	2.38 (1.02–5.55), $p = 0.04$	2.37 (1.02–5.54), $p = 0.04$

Abbreviations: SOFA, Sequential Organ Failure Assessment; PaO_2, arterial oxygen partial pressure; FiO_2, fraction of inspired oxygen.

limited training in MV and limited knowledge of the risk of hyperoxemia.

In the present study, neither hyperoxemia, nor excess oxygen use were independently associated with mortality. Our results with ARDS COVID-19 patients are in accordance with those found in the LUNG SAFE study, in which ARDS non-COVID-19 patients were assessed.[7] Recently, two randomized clinical trials ($LOCO_2$ and HOT-ICU) also failed to show differences in mortality in hypoxemic acute respiratory failure patients who underwent conservative or liberal oxygen therapy.[9,10] A post hoc analysis of the HOT-ICU trial with COVID-19 patients only did not show a statistically significant difference in mortality between a lower and a higher oxygenation target.[14] Conversely, an analysis of the results of 10 trials conducted by the ARDS Network showed that higher oxygen exposure, defined as FiO_2 higher than 0.5 with PaO_2 higher than 80 mmHg was associated with lower ventilator-free days and higher mortality.[15] The reasons for those conflicting results might include different clinical characteristics and severity among included patients, who may have different oxygen demands, and different levels of hyperoxemia that occurred in the studies. Negative impact on patients outcomes might occur as a result of higher levels or more extended periods of exposure to hyperoxemia.[16,17] Those results showed that a more conservative oxygen use in mechanically ventilated patients is feasible, safe, and can reduce the harmfulness associated with hyperoxemia. Moreover, this strategy reduces costs and spare oxygen, a gas that became scarce in some regions during the COVID-19 pandemic.

This study has several limitations. 1. Patients were not randomized to the groups but selected according to the ICU where they were admitted. Therefore, confounding variables other than admission in an ICU with a FiO_2 protocol might have contributed to the occurrence of hyperoxemia and excessive oxygen use. 2. Since a convenience sample was used, without sample size calculation, this study may have had limited power to detect associations between hyperoxemia or excess oxygen use and mortality. 3. Data were collected once, at a standardized time each morning, on the first two days of MV. Consequently, these data may not properly reflect neither the different values of FiO_2 and PaO_2 over the course of those days, nor those values over the following days of MV. 4. Data were obtained in only two ICUs, which limits the extrapolation of the results to other ICUs.

In conclusion, our findings showed that hyperoxemia and excess oxygen use may be prevalent in COVID-19 patients mechanically ventilated and that following FiO_2 adjustment protocol can reduce those two events. Even though hyperoxemia and excess oxygen use were not associated with worse clinical outcomes, adopting a FiO_2 protocol is safe and may be useful in a scenario of depleted oxygen resources, as was seen during the COVID-19 pandemic.

Author contributions

- Edimar Pedrosa Gomes: conception and design of the study; acquisition of data; analysis and interpretation of data; drafting the article; final approval of the version to be published.
- Maycon Moura Reboredo: conception and design of the study; analysis and interpretation of data; drafting the article; final approval of the version to be published.
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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.medin.2022.04.004.

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