Javier Hernán Dorado[1], Joaquín Pérez[1], Emiliano Navarro[2], Emiliano Gogniat[3], Sebastían Torres[1], Sabrina Cagide[1], Matías Accoce[1,4]

Impact of liberal *versus* conservative saturation targets on gas exchange indices in COVID-19 related acute respiratory distress syndrome: a physiological study

Impacto de alvos de saturação liberais versus conservadores sobre os índices de troca gasosa na síndrome do desconforto respiratório agudo relacionada à COVID-19: um estudo fisiológico

1. Sanatorio Anchorena San Martín - Buenos Aires, Argentina.
2. Centro del Parque - Buenos Aires, Argentina.
3. Capítulo de Kinesiología Intensivista, Sociedad Argentina de Terapia Intensiva -Buenos Aires, Argentina.
4. Facultad de Medicina y Ciencias de la Salud, Universidad Abierta Interamericana - Buenos Aires, Argentina.

ABSTRACT

Objective: To compare gas exchange indices behavior by using liberal *versus* conservative oxygenation targets in patients with moderate to severe acute respiratory distress syndrome secondary to COVID-19 under invasive mechanical ventilation. We also assessed the influence of high FiO_2 on respiratory system mechanics.

Methods: We prospectively included consecutive patients aged over 18 years old with a diagnosis of COVID-19 and moderate-severe acute respiratory distress syndrome. For each patient, we randomly applied two FiO_2 protocols to achieve SpO_2 88% - 92% or 96%. We assessed oxygenation indices and respiratory system mechanics.

Results: We enrolled 15 patients. All the oxygenation indices were significantly affected by the FiO_2 strategy ($p < 0.05$) selected. The PaO_2/FiO_2 deteriorated, $PA\text{-}aO_2$ increased and Pa/AO_2 decreased significantly when using FiO_2 to achieve SpO_2 96%. Conversely, the functional shunt fraction was reduced. Respiratory mechanics were not affected by the FiO_2 strategy.

Conclusion: A strategy aimed at liberal oxygenation targets significantly deteriorated gas exchange indices, except for functional shunt, in COVID-19-related acute respiratory distress syndrome. The respiratory system mechanics were not altered by the FiO_2 strategy.

Keywords: COVID-19; Coronavirus infections; Respiratory distress syndrome; Respiration, artificial; Oxygenation; Pulmonary gas exchange; Respiratory mechanics

Clinical Trials Register: NCT04486729

Conflicts of interest: None.

Submitted on December 21, 2020
Accepted on August 7, 2021

Corresponding author:
Javier Hernán Dorado
Sanatorio Anchorena de San Martin
Perdriel 4189 - Villa Lynch
Buenos Aires, Argentina
E-mail: javierhdorado@gmail.com

Responsible editor: Alexandre Biasi Cavalcanti

DOI: 10.5935/0103-507X.20210081

INTRODUCTION

The novel infection caused by coronavirus-19 (COVID-19) has been recently recognized and has spread throughout China and most countries around the world. Almost 25 million people were infected worldwide by August 27, 2020, and the number of deaths has risen to more than 820,000.[1]

Approximately 85% of COVID-19-infected patients admitted to the intensive care unit (ICU) develop severe acute respiratory syndrome (SARS-CoV-2).[2] However, despite meeting acute respiratory distress syndrome (ARDS) criteria, the pathophysiological features and clinical course of SARS-CoV-2 may differ substantially from those of classical ARDS.[3,4]

According to the Berlin definition, the severity of ARDS is determined by the degree of gas exchange compromise.[3] Consequently, the quantification of oxygenation indices is considered mandatory. In particular, the quotient of partial pressure of oxygen and fraction of inspired oxygen (PaO_2/FiO_2) is the oxygenation index most widely used in daily clinical practice due to its availability and ease of interpretation. Furthermore, the PaO_2/FiO_2 value is a determinant to guide the implementation of rescue therapies such as high positive end expiratory pressure (PEEP), neuromuscular blocking agents,[5] prone positioning[6] or extracorporeal membrane oxygenation.[7] However, the PEEP level, the stabilization time after adjusting ventilatory settings, the time after ARDS onset and the FiO_2 selected when obtaining arterial blood gases have all been shown to significantly influence the PaO_2/FiO_2 value.[8]

In clinical practice at the bedside, FiO_2 selection is based on pulse oximeter saturation (SpO_2). The most relevant ARDS clinical trials published in the last two decades set FiO_2 to obtain a SpO_2 between 88 - 95%.[5-7,9] However, some controversies exist regarding the benefits and harms of liberal *versus* conservative oxygenation approaches in patients with classical ARDS during controlled mechanical ventilation.[10,11] In this setting, the surviving sepsis campaign recently recommended a SpO_2 between 92% and 96% in ARDS caused by COVID-19.[2] Considering the particular pathophysiological features of SARS-CoV-2, FiO_2 selection may considerably impact the oxygenation indices and affect clinical decisions. Furthermore, high concentrations of oxygen might alter the respiratory system mechanics through reabsorption atelectasis formation and augment the stress applied over the lung, thus promoting ventilator-induced lung injury.

The aim of this study was to compare gas exchange indices behavior by using liberal *versus* conservative oxygenation targets in patients with moderate to severe ARDS secondary to COVID-19 under invasive mechanical ventilation. Second, we assessed the influence of high FiO_2 on respiratory system mechanics to evaluate the impact of reabsorption atelectasis on lung stress.

METHODS

We conducted a prospective physiological study in the ICU of *Sanatorio Anchorena San Martín*. The local Review Board approved the protocol (committee's reference number: 16/2020), and all of the patients' next of kin signed informed consent forms. This is a preliminary report of clinicaltrial.gov NCT number: NCT04486729.

We included all consecutive patients admitted to our ICU aged over 18 years old with a confirmed diagnosis of COVID-19 (positive polymerase chain reaction through nasopharyngeal swab) and moderate to severe ARDS according to the Berlin definition.[3] Other inclusion criteria were invasive mechanical ventilation requirement for less than 72 hours before enrollment and the need of neuromuscular blocking agents by medical decision. Based on previous physiological studies with similar methodologies and designs, we planned to include a sample size of 15 patients.[12] The exclusion criteria were hemodynamic instability despite fluid resuscitation and vasopressor support, previous diagnosis of chronic obstructive pulmonary disease, no drained pneumothorax, intracranial hypertension, pregnancy, thoracic chest wall abnormalities, bronchopleural fistula and contraindications to esophageal catheter insertion.

Baseline characteristics and laboratory analysis of all patients were retrieved from our electronic clinical records. We collected the variables age, sex, number of days under invasive mechanical ventilation, Simplified Acute Physiology Score II (SAPS II) at admission, ARDS severity and sequential organ failure assessment (SOFA) score the day of enrollment.

Respiratory mechanics

We evaluated respiratory system mechanics using a specific device and software (Fluxmed, MBMed®, Buenos Aires, Argentina) connected to a personal computer. The flow (F) and volume (Vol) were measured with a flow sensor provided by the manufacturer that was correctly calibrated. We inserted an esophageal balloon (MBMed® VA-A-008, nonlatex) 7 cm in length filled with 0.5mL of air. The correct position in the lower third of the esophagus was confirmed by the presence of cardiac artifacts and the occlusion test as previously described elsewhere.[13] We performed end inspiratory and end expiratory occlusions of at least two seconds, and we evaluated the following variables: plateau pressure (P_{plat}), driving airway pressure (ΔP_{aw}), inspiratory esophageal pressure (P_{es} insp), expiratory esophageal pressure (Pes exp), driving esophageal pressure (ΔP_{es}), inspiratory transpulmonary pressure using the direct method ($P_{L\text{-}direct}$ insp), expiratory transpulmonary pressure (P_L exp), driving transpulmonary pressure (ΔP_L) and inspiratory transpulmonary pressure using the elastance-derived method ($P_{L\text{-}elas}$ insp) using the formula:

$P_{L\text{-}elas}$ insp = Plateau pressure x (lung elastance/respiratory system elastance).

The respiratory system elastance (E_{rs}), chest wall elastance (E_{cw}) and lung elastance (E_L) were calculated with the following formulas:

$E_{rs} = \Delta Paw/\Delta Vol$ (Expired volume in L);
$E_{cw} = \Delta Pes/\Delta Vol(L)$;
$E_L = \Delta P_L/\Delta Vol(L)$.

Oxygenation indices

The PaO_2/FiO_2 index was calculated as PaO_2 (mmHg)/FiO_2.[14] To calculate other oxygenation indices, we used the equation of partial pressure of alveolar oxygen (PAO_2) = ((Pbarometric - PvH_2O) x FiO_2) - PCO_2/RQ,[14] where Patm is the barometric pressure expressed in mmHg (760), PvH_2O is the partial pressure of water steam expressed in mmHg (47), $PaCO_2$ is the partial pressure of arterial carbon dioxide and RQ is the respiratory quotient (0.8). Once PAO_2 was obtained, we calculated the indices alveolar-arterial oxygen pressure gradient ($PA\text{-}aO_2$) and the quotient arterial/alveolar pressure of oxygen (Pa/AO_2).

The functional shunt fraction was calculated based on venous admixture determination, considering central venous oxygen saturation ($ScVO_2$) as an acceptable surrogate for mixed venous oxygen saturation: $Qs/Qt = (CcO_2 - CaO_2)/(CcO_2/CvO_2)$, where CaO_2, CvO_2, and CcO_2 are the arterial, venous and capillary oxygen contents, respectively. [14] When available, mixed venous blood was obtained from a Swan Ganz catheter.

Procedure

All patients were deeply sedated with propofol and fentanyl and paralyzed with atracurium. The subjects were ventilated in semirecumbent position in volume control mode with a tidal volume 6mL/kg of predicted body weight, square flow waveform with 0.3 seconds of end inspiratory pause, respiratory rate between 15 - 35 breaths per minute, aiming to achieve a pH between 7.20 - 7.45. The PEEP value was $5cmH_2O$.

We randomly applied two different FiO_2 strategies to each patient: one strategy to achieve a liberal (96%) SpO_2 and one to obtain a conservative (88 - 92%) SpO_2, both periods evaluated on the same day. For randomization, we used the software available on the randomization.com website, and we used closed opaque envelopes. Each phase lasted 10 minutes, based on the study carried out by Cakar et al., in which they showed that 5 minutes was enough time to achieve a stable PaO_2 level.[15] After the end of each period, we obtained arterial and mixed venous blood samples and monitored the respiratory system mechanics. We did not use a washout period between each phase because of aspects related to the viability and safety of the patients included. Considering the critical status of our sample and the wide variety of factors that could affect arterial oxygenation (including basic care such as mobilization, aspiration of secretions, positional changes), extending the time of measurements would have led to limiting these interventions for longer periods of time, affecting the standard of care in our unit and the patient´s clinical status.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) and number (percentage), as appropriate. The Shapiro-Wilk test was used to test normality. One sample Student`s t-test was used to assess the statistical significance of the difference between the two conditions when the data were normally distributed; otherwise, the Wilcoxon test was used. The results with a two-tailed $p \leq 0.05$ were considered statistically significant. The statistical analysis was performed with R 4.0.3 (R Foundation for Statistical Computing - www.rproject.org) and the ggplot2 package.

RESULTS

We enrolled 15 patients. The mean age was 55.6 years old, and 73.3% of patients were men with SAPS II 32 and SOFA 6.2 at admission (Table 1). Three subjects were classified as severe ARDS, and twelve were classified as having moderate ARDS. The median (interquartile range) of days between intubation and enrollment was 1 (1 - 3). The liberal oxygenation phase could not be completed in one patient due to desaturation despite using FiO_2 1.

The mean ± SD FiO_2 and SpO_2 for liberal and conservative oxygenation targets were 0.80 ± 0.19 and 96% ± 1 and 0.40 ± 0.13 and 89% ± 3, respectively.

The comparisons between oxygenation indices obtained with liberal *versus* conservative oxygenation targets are presented in figure 1. All of the indices were significantly affected by FiO_2 selection. The PaO_2/FiO_2 deteriorated (FiO_2 liberal; mean = 140.9 ± 34.0, FiO_2 conservative; mean = 165 ± 54.4; p = 0.015), $PA\text{-}aO_2$ increased (FiO_2 liberal; mean = 397.5 ± 133; FiO_2 conservative; mean = 190.4 ± 139.7; p < 0.001) and Pa/AO_2 decreased (FiO_2 liberal; mean = 0.22 ± 0.06; FiO_2 conservative;

Table 1 - Baseline characteristics of the patients

Variables	
Demographic variables	
Female sex	4/15
Age	55.6 ± 9.4
APACHE II	13.1 ± 5
SAPS II	32 (10.8)
Respiratory variables	
Tidal volume (mL/kg)	6.1 ± 0.4
PEEP (cmH_2O)	10.9 (10.5 - 12.5)
FiO_2	0.45 (0.35 - 0.52)
Airway driving pressure (cmH_2O)	10.5 (9.55 - 11.6)
Gas exchange	
PaO_2/FiO_2	147.4 (125.5 - 179)
Functional Qs/Qt	0.34 ± 0.11
Moderate ARDS, n/total	12/15
ICU mortality, (n/total)	6/15

APACHE II - Acute Physiology and Chronic Health Evaluation II; SAPS II - Simplified Acute Physiology Score; PEEP - positive end expiratory pressure; FIO_2 - inspired fraction of oxygen; PaO_2/FiO_2 - partial pressure of oxygen/inspired fraction of oxygen; Qs/Qt - functional shunt fraction; ARDS - acute respiratory distress syndrome; ICU - intensive care unit. Data expressed as n/total, mean ± standard deviation, median (interquartile range).

mean = 0.31 ± 0.13; p = 0.002) significantly by using FiO_2 to achieve SpO_2 96%. Conversely, the functional shunt fraction was reduced (FiO_2 liberal; mean = 0.40 ± 0.08, FiO_2 conservative; mean = 0.45 ± 0.13; p = 0.040).

The variables related to the respiratory mechanics are presented in table 2. There were no significant changes in mechanical variables between the conservative and liberal SpO_2 strategies.

DISCUSSION

Our findings show that adopting a liberal SpO_2 target considerably affects the oxygenation indices, which may have implications not only in severity stratification of ARDS but also in the clinical decision-making process.

A proper stabilization time and standardized ventilatory settings have been shown to improve the severity stratification in classical ARDS.[6] Villar et al. found that selecting an FiO_2 of 0.5 with the aim of achieving an SpO_2 not less than 88% allows to better identify patients at risk of death in comparison with higher fractions of inspired oxygen.[8] In patients with a high percentage of shunt and low ventilation/perfusion (V/Q) units, increasing the oxygen supply significantly affects the gas exchange indices due to the marginal effect on PaO_2 of higher concentrations of PAO_2.[16]

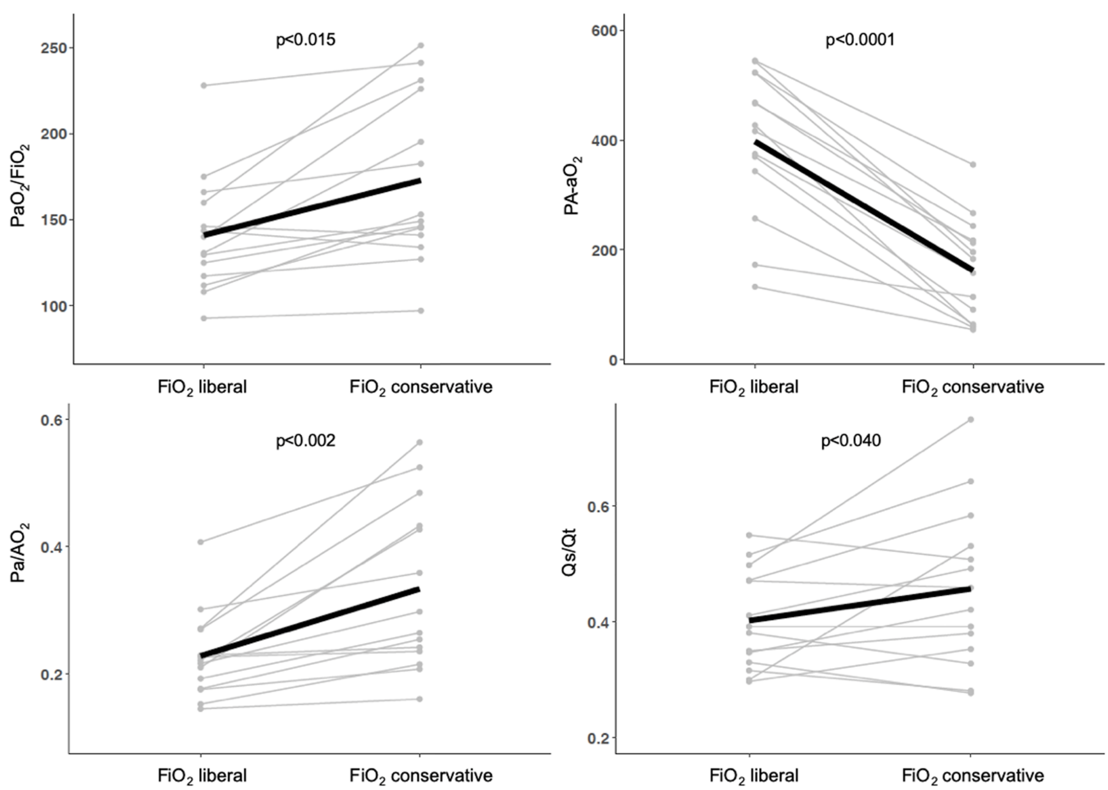

Figura 1 - Oxygenation indices behavior with liberal and conservative oxygenation strategies.

PaO_2/FiO_2 - partial pressure of oxygen/inspired fraction of oxygen; $PA\text{-}_aO_2$ - alveolar-arterial oxygen pressure gradient; Pa/AO_2 - quotient arterial/alveolar pressure of oxygen; Qs/Qt - functional shunt fraction.

Indeed, perfused and ventilated alveoli present limited capacity to increase CaO_2, as explained by the classic behavior of the hemoglobin dissociation curve. Hence, deterioration in $PA\text{-}aO_2$ and Pa/AO_2 is somewhat expected considering that theoretical PAO_2 will rise in the same proportion that FiO_2 is changed (provided that $PaCO_2$ is constant), but PO_2 will not because deoxygenated blood leaving low V/Q units will mix with oxygenated blood coming from normal V/Q units.[17] The patients included in our study presented a 40% functional shunt average, which explains why, even in COVID-19, where pathophysiological features may differ from classical ARDS, the application of high oxygen concentrations affected the gas exchange indices in a similar way to previous descriptions.[14,16,18]

The LOCO II trial recently found survival benefits at 90 days and fewer mesenteric ischemic events approaching a liberal oxygenation strategy in typical ARDS. The control group received lower PEEP and considerably less prone positioning trials, which could be explained by the fact that both interventions were decided based on the PaO_2/FiO_2 value.[11] Our study suggests that using liberal SpO_2 strategies may increase the need of rescue therapies to treat the refractory hypoxemia consequences of a remarkable deterioration of the PaO_2/FiO_2 index in this context. In our study, three patients changed their severity of ARDS from moderate to mild, and other three subjects increased their PaO_2/FiO_2 above 150mmHg only by using a lower FiO_2, a situation that has been reported previously in non-COVID-19-related ARDS.[18] Moreover, only two patients required less than 0.6 FiO_2 to achieve at least an SpO_2 of 96%, which should warns about the adverse effects of exposing the alveolar gas barrier to high concentrations of oxygen for long periods of time.

In conventional ARDS, atelectasis caused by superimposed pressure and lung volume reduction represent the main mechanisms of hypoxemia, showing a direct relationship between Qs/Qt and PaO_2/FiO_2 after adjusting for Crs.[19] The same reasoning does not hold completely true for COVID-19-related ARDS. Our initial hypothesis was that high FiO_2 would increase Qs/Qt secondary to reabsorption atelectasis and the reversal of hypoxic vasoconstriction.[20] Our results showed the opposite, which could be explained by three potential reasons. First, respiratory system mechanics, in particular, lung stress (PL-elas insp and PL-direct insp) remained unchanged after increasing FiO_2, which might indicate that atelectasis formation was not significant, possibly due to the limited time of exposure as well as the use of FiO_2 lower than 100%. Second, the impairment of the normal mechanisms of hypoxemic vasoconstriction has been proposed as a possible cause to explain the profound hypoxemia in COVID-19 in the absence of significant alterations of respiratory mechanics;[21-23] thus, increasing FiO_2 could not have had considerable effects on vasomotor tone. Third, an adequate evaluation of shunt fraction implies the application of FiO_2 100%, a condition that was not accomplished because it was not the aim of our study. Setting $FiO_2 < 100\%$ not only assesses the real shunt fraction but also includes those units with a low V/Q ratio in the Qs/Qt calculation.[17] It is expected that increasing FiO_2 will ameliorate the influence of low V/Q units, making the true shunt fraction more visible. Grasso et al. found a high proportion of Qs/Qt (> 40%) when assessing functional shunt with an FiO_2 lower than 100%; when pure oxygen was used, the real shunt fraction was only 4%.[24]

Table 2 - Respiratory mechanics behavior with liberal and conservative oxygenation strategies

Variable	FiO_2 conservative (T1)	FiO_2 liberal (T2)	T1 - T2 (95%CI)	p value
ΔP_{aw}	10.0 ± 1.5	9.9 ± 1.5	-0.1 (-0.2 - 0.4)	0.579
P_{plat}	16.1 ± 2.2	16.2 ± 2.3	-0.1 (-0.3 - 0.4)	0.682
ΔP_L	8.1 ± 1.7	8.0 ± 1.8	0.1 (-0.4 - 0.7)	0.582
ΔP_{es}	1.9 ± 0.9	1.9 ± 0.7	0.0 (-0.4 - 0.3)	0.258
P_L exp	-3.2 ± 3.4	-2.6 ± 3.2	-0.2 (-0.3 - 0.6)	0.768
$P_{L\text{-}elas}$ insp	13.0 ± 2.6	13.1 ± 2.4	0.1 (-0.6 - 0.9)	0.741
$P_{L\text{-}direct}$ insp	4.7 ± 3.1	5.3 ± 3.1	0.4 (-0.3 - 1.1)	0.280
E_{rs}	26.2 ± 6.2	25.4 ± 5.1	0.2 (-0.7 - 1.1)	0.598
E_L	20.8 ± 5.5	20.4 ± 5.0	-0.4 (-0.9 - 1.8)	0.498
E_{cw}	5.3 ± 2.7	4.9 ± 2.1	-0.2 (-1.1 - 0.7)	0.620
E_L/E_{rs}	0.79 ± 0.08	0.80 ± 0.08	0.01(-0.03 - 0.04)	0.839

FIO_2 - inspired fraction of oxygen; 95%CI - 95% confidence interval; ΔP_{aw} - driving airway pressure; P_{plat} - plateau pressure; ΔP_L - driving transpulmonary pressure; ΔP_{es} - driving esophageal pressure; P_L exp - expiratory transpulmonary pressure; $P_{L\text{-}elas}$ insp - inspiratory transpulmonary pressure using elastance derived method; $P_{L\text{-}direct}$ insp - inspiratory transpulmonary pressure, direct method; E_{rs} -respiratory system elastance; E_L - lung elastance; E_{cw} - chest wall elastance. Data expressed in mean ± standard deviation and absolute difference (confidence interval).

Our study presents several limitations that must be addressed. First, the small number of patients enrolled in our study does not allow us to make conclusions regarding the best clinical strategy in terms of outcome benefits. On the other hand, cardiac output was not monitored during the protocol, and a reduction in the functional shunt when FiO_2 was increased might be a feasible consequence of the reduction in cardiac output secondary to improvement in CaO_2. Finally, all of the measurements were carried out with a PEEP of 5cmH_2O and the behavior of gas exchange indices when varying FiO_2 may be different with higher PEEP levels. However, this scenario is more physiologically attractive for assessing the effects of different FiO_2 values considering that low PEEP exacerbates the loss of lung volume and increases the proportion of low V/Q units and functional shunt and, thus, the possible activation of hypoxia-induced vasoconstriction.[25] In addition, the Berlin definition of ARDS not only defines but also stratifies the severity of the condition using a level of PEEP equal to or greater than 5cmH2O.[3] In addition, several physiological studies have advocated using low PEEP levels to more accurately assess ARDS severity.[25-28] Higher levels of PEEP might mask the severity of the underlying lung injury and impact the assessment of lung recruitability, and, therefore, hinder the prediction of the response to therapeutic interventions such as recruitment maneuvers or prone positioning.[25]

CONCLUSION

A strategy aimed at liberal oxygenation targets significantly deteriorated gas exchange indices, except for functional shunt, compared with a conservative strategy in COVID-19 related acute respiratory distress syndrome during invasive mechanical ventilation. The respiratory system mechanics were not altered by the fraction of inspired oxygen strategy.

AUTHORS' CONTRIBUTIONS

J. H. Dorado participated in conceptualization, formal analysis investigation; was the project administrator and supervised, collected, analyzed and interpreted the patient data; the major contributor to the writing process.

J. Pérez participated in conceptualization and formal analysis investigation; collected, analyzed and interpreted the patient data; and was a contributor to the writing process.

E. Navarro participated in formal analysis investigation and analyzed and interpreted the patient data.

E. Gogniat participated in conceptualization and formal analysis investigation and analyzed and interpreted the patient data.

S. Torres participated in conceptualization and formal analysis investigation; collected the patient data and was a contributor to the writing process.

S. Cagide participated in conceptualization and formal analysis investigation; collected the patient data; was a contributor to the writing process.

M. Accoce participated in conceptualization, formal analysis investigation and supervision; collected, analyzed and interpreted the patient data; was a contributor to the writing process.

All authors read and approved the final manuscript.

RESUMO

Objetivo: Comparar o comportamento dos índices de troca gasosa conforme o uso de alvos de oxigenação liberais em comparação a conservadores em pacientes com síndrome do desconforto respiratório agudo moderada a grave secundária à COVID-19 e em uso de ventilação mecânica; avaliar a influência da FiO_2 elevada na mecânica do sistema respiratório.

Métodos: Foram incluídos prospectivamente pacientes consecutivos com idades acima de 18 anos, diagnóstico de COVID-19 e síndrome do desconforto respiratório agudo moderada e grave. Para cada paciente, aplicou-se aleatoriamente dois protocolos de FiO_2 para obter SpO_2 de 88% a 92% ou 96%. Avaliaram-se os índices de oxigenação e a mecânica do sistema respiratório.

Resultados: Foram incluídos 15 pacientes. Todos seus índices foram significantemente afetados pela estratégia de FiO_2 ($p < 0,05$). A proporção PaO_2/FiO_2 deteriorou, o $PA\text{-}aO_2$ aumentou e o Pa/AO_2 diminuiu significantemente com a utilização de FiO_2 para obter SpO_2 96%. Opostamente, a fração de *shunt* funcional foi reduzida. A mecânica respiratória não foi afetada pela estratégia de FiO_2.

Conclusão: Uma estratégia com alvos liberais de oxigenação deteriorou significantemente os índices de troca gasosa, com exceção do *shunt* funcional, em pacientes com síndrome do desconforto respiratório agudo relacionada à COVID-19. A mecânica do sistema respiratório não foi alterada pela estratégia de FiO_2.

Descritores: COVID-19; Infecções por coronavírus; Síndrome do desconforto respiratório; Respiração artificial; Oxigenação; Troca gasosa pulmonar; Mecânica respiratória

Registro Clinical Trials: NCT04486729

REFERENCES

1. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811-8.
2. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med. 2020;46(5):854-87.
3. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-33.
4. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099-102.
5. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107-16.
6. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159-68.
7. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, Da Silva D, Zafrani L, Tirot P, Veber B, Maury E, Levy B, Cohen Y, Richard C, Kalfon P, Bouadma L, Mehdaoui H, Beduneau G, Lebreton G, Brochard L, Ferguson ND, Fan E, Slutsky AS, Brodie D, Mercat A; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018;378(21):1965-75.
8. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, Santos-Bouza A, Fernández RL, Kacmarek RM; Spanish Initiative for Epidemiology, Stratification, and Therapies for ARDS (SIESTA) Network. A universal definition of ARDS: the PaO_2/FiO_2 ratio under a standard ventilatory setting--a prospective, multicenter validation study. Intensive Care Med. 2013;39(4):583-92.
9. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301-8.
10. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S, Freebairn R, King V, Linke N, Litton E, McArthur C, McGuinness S, Panwar R, Young P; ICU-ROX Investigators the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med. 2020;382(11):989-98.
11. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, Quenot JP, Pili-Floury S, Bouhemad B, Louis G, Souweine B, Collange O, Pottecher J, Levy B, Puyraveau M, Vettoretti L, Constantin JM, Capellier G; LOCO2 Investigators and REVA Research Network. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med. 2020;382(11):999-1008.
12. Mauri T, Spinelli E, Scotti E, Colussi G, Basile MC, Crotti S, et al. Potential for lung recruitment and ventilation-perfusion mismatch in patients with the acute respiratory distress syndrome from Coronavirus Disease 2019. Crit Care Med. 2020;48(8):1129-34.
13. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, Guérin C, Patroniti N, Ranieri VM, Gattinoni L, Nava S, Terragni PP, Pesenti A, Tobin M, Mancebo J, Brochard L; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med. 2014;189(5):520-31.
14. Aboab J, Louis B, Jonson B, Brochard L. Relation between PaO2/FIO2 ratio and FIO_2: a mathematical description. Intensive Care Med. 2006;32(10):1494-7.
15. Cakar N, Tuŏrul M, Demirarslan A, Nahum A, Adams A, Akýncý O, et al. Time required for partial pressure of arterial oxygen equilibration during mechanical ventilation after a step change in fractional inspired oxygen concentration. Intensive Care Med. 2001;27(4):655-9.
16. Zetterström H. Assessment of the efficiency of pulmonary oxygenation. The choice of oxygenation index. Acta Anaesthesiol Scand. 1988;32(7):579-84.
17. Wagner PD. The physiological basis of pulmonary gas exchange: implications for clinical interpretation of arterial blood gases. Eur Respir J. 2015;45(1):227-43.
18. Karbing DS, Kjaergaard S, Smith BW, Espersen K, Allerød C, Andreassen S, et al. Variation in the PaO2/FiO2 ratio with FiO2: mathematical and experimental description, and clinical relevance. Crit Care. 2007;11(6):R118.
19. Chiumello D, Busana M, Coppola S, Romitti F, Formenti P, Bonifazi M, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. Intensive Care Med. 2020;46(12):2187-96.
20. Santos C, Ferrer M, Roca J, Torres A, Hernández C, Rodriguez-Roisin R. Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med. 2000;161(1):26-31.
21. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020;46(6):1099-102.
22. Gattinoni L, Meissner K, Marini JJ. The baby lung and the COVID-19 era. Intensive Care Med. 2020;46(7):1438-40.
23. Patel BV, Arachchillage DJ, Ridge CA, Bianchi P, Doyle JF, Garfield B, et al. Pulmonary angiopathy in severe COVID-19: physiologic, imaging, and hematologic observations. Am J Respir Crit Care Med. 2020;202(5):690-9.
24. Grasso S, Mirabella L, Murgolo F, Di Mussi R, Pisani L, Dalfino L, et al. Effects of Positive End-Expiratory Pressure in "High Compliance" Severe Acute Respiratory Syndrome Coronavirus 2 Acute Respiratory Distress Syndrome. Crit Care Med. 2020;48(12):e1332-6.
25. Caironi P, Carlesso E, Cressoni M, Chiumello D, Moerer O, Chiurazzi C, et al. Lung recruitability is better estimated according to the Berlin definition of acute respiratory distress syndrome at standard 5 cm H2O rather than higher positive end-expiratory pressure: a retrospective cohort study. Crit Care Med. 2015;43(4):781-90.
26. Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med. 2011;37(10):1595-604.
27. Karbing DS, Panigada M, Bottino N, Spinelli E, Protti A, Rees SE, et al. Changes in shunt, ventilation/perfusion mismatch, and lung aeration with PEEP in patients with ARDS: a prospective single-arm interventional study. Crit Care. 2020;24(1):111.
28. Cressoni M, Caironi P, Polli F, Carlesso E, Chiumello D, Cadringher P, et al. Anatomical and functional intrapulmonary shunt in acute respiratory distress syndrome. Crit Care Med. 2008;36(3):669-75.