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Prone position in severe hypoxemia in patients with covid-19 during venovenous ECMO, does the number of cycles matter?

Abstract

Extracorporeal membrane oxygenation (ECMO) support has been known to be beneficial in cases of severe Adult Respiratory Distress Syndrome (ARDS). Theincrease in such cases results in an increase in scenarios of severe hypoxemia even during an ECMO run. The purpose of this study was to evaluate the benefit of the proneposition (PP) in an analytical observational retrospective cohort study. The studyincluded adult patients with ARDS, caused as a result of SARS-CoV-2, undergoing PPduring ECMO support in the period from 2020 to 2021. Thirty-five patients were placedin PP with an average of 3.6 cycles per patient. The group of patients undergoing >3 PP cycles had a significant improvement in oxygenation during PP, PaO_2 (60.13 vs. 66.15, mmHg $p = 0.0065$) and PaO_2/FiO_2 (136 vs. 155, $p = 0.0026$). After adjusting forconfounding variables (age, RESP score, and days from the start of ECMO and the firstcycle of PP), the group with >3 cycles showed a hazard ratio of 0.2 (95% confidence interval, 0.051–0.78; $p = 0.02$). The study outcomes confirmed the benefits of PP as a strategy against severe hypoxemia in ECMO, and evaluated variables such as the number of cycles, which may be associated with improved survival in this subgroup of critically ill patients.

Keyword: Prone position, Extracorporeal membrane oxygenation, severe hypoxemia, survival

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Introduction

Prone position (PP) is a recommended support strategy in patients with moderate to severe adult respiratory distress syndrome (ARDS). In spite of reducing the distensibility of the rib cage, owing to a reduction in the abdominal expansion and to the fact that theposterior thoracic wall of the rib cage is less compliant, PP generates a more homogeneous distribution of stress and strain on the lung parenchyma. This consequently decreases the hyperinflation risk of non-dependent lung regions while reducing atelectrauma of dependent lung regions. This increase in alveolar recruitmentis achieved because the dorsal lung mass is greater than the ventral one, thereby acquiring a better distribution (V/Q). This is attributable to the fact that perfusion is maintained mainly in the dorsal regions when the patient is in the PP.[1]

Moderate to severe ARDS was defined as a ratio of PaO_2/FiO_2 of <150, with a FiO_2 of at least 0.6, a positive end-expiratory pressure (PEEP) of at least 5 cmH_2O, and a tidalvolume (VT) close to 6 mL per kilo of ideal weight. In these patients, PP for mean duration of 17 hours increased the rate of successful extubation and, most importantly, reduced the 28-day mortality from 32.8% in the supine group to 16% in the prone group ($p < 0.001$), despite showing no variations in the time of mechanical ventilation (MV) and ICU stay.[2]

Venovenous (VV) ECMO (ExtraCorporeal Membrane Oxygenation) is a rescue supportagainst severe ARDS refractory to conventional strategies, which provides complete blood oxygenation, eliminates CO_2 retention, while allowing a lung-protective and resting MV that minimizes the risk of ventilator-induced lung injury. Early initiation of this supporttherapy leads to a 90-day mortality reduction and to a reduced therapeutic failure whencompared with conventional ventilatory support.[3]

Owing to disease severity and the extensive pulmonary compromise, the patient may present severe hypoxemia in spite of the support provided by the VV ECMO, even underthis extracorporeal support. In the face of this scenario, there were strategies aimed at improving oxygenation, such as increasing oxygen content (increasing ECMO blood flow or hemoglobin level), reducing recirculation (distance between cannulas or changeof cannulation configuration), reducing oxygen consumption (sedation, neuromuscular relaxation, or therapeutic hypothermia), reducing cardiac output (beta-blockers), or reducing intrapulmonary shunt, for which PP has been a widely used maneuver.[4]

Taking into account a significant percentage of prone patients during ECMO support inour institution, it is necessary to objectively consider the variation observed with the PPand the number of prone cycles, the gasometric parameters, ventilatory mechanics variables, and the survival.

Materials and methods

An analytical observational retrospective cohort study was designed. Using non- probabilistic convenience sampling, a total of 35 patients with SARS-CoV-2 and ARDS,aged ≥18 years, defined under the Kigali/Berlin criteria, placed in the PP during ECMOsupport and treated during the period 2020–2021, were included.

Data were obtained from the registry database of patients who required ECMO support because of SARS-CoV-2 at Fundación Clínica Shaio, a high-complexity institution in Bogotá DC, and a center of reference and excellence in Colombia, recognized by the *s*. With protocols for initiation of VV ECMO support against severe hypoxemia (PaO_2/FiO_2 < 80) or severe hypercapnia (pH < 7.20 and $PaCO_2$ > 80 mmHg) with fewerthan 10 days of mechanical ventilation and refractory to conventional management including: sedation for RASS of −5, neuromuscular relaxation, protective MV and PP. The standard VV ECMO configuration is percutaneous insertion of a femoral venous drainage cannula and a jugular venous cannula for

venous return with blood flow parameters of 60–80 mL/kg, delivered fraction of inspired O_2 of 100% and sweep gas in a 1:1 ratio to blood flow.

Most patients on ECMO receive pressure-controlled ventilation at our institution, with the aim of ensuring protective ventilation. The decision to use the PP was made according to medical judgment in cases of severe hypoxemia with clinical implications. Prior to the PP maneuver, target RASS of −5 and adequate neuromuscular blockade are guaranteed. The procedure was performed by a multidisciplinary team of at least 6people. During PP, postural changes are guaranteed every 2 hours to avoid skin injury and peripheral nerve damage; prone cycles are extended from 16 hours of PP to 6 hours of supine positioning. The decision to complete the PP cycles was also a clinical decision.

COVID-19 virus was detected in a nasal swab sample collected in 1.3 mL of transport medium with a 0.3 mL minimum sample volume, according to the institutional protocol for COVID-19 tests, for subsequent molecular analysis by FilmArray BioFire COVID-19.

Variables of interest

The following demographic and medical variables were collected for all patients: age, body mass index (BMI), RESP severity score (*Respiratory ECMO Survival Prediction)*, days of MV assessed at ECMO support initiation; sex; days between ECMO initiation and the first PP cycle.

Once on VV ECMO support, programming and variables in mechanical ventilation werecollected: PEEP, control pressure (CP), respiratory rate (RR), tidal volume (VT), peak pressure (PIP), plateau pressure, driving pressure and lung compliance; blood gasometry (pH,PaO_2/FiO_2, HCO_3, and CO_2) variables collected in each patient 1 hour before and 6 hours after each PP cycle. Additionally, the number of PP cycles during ECMO was obtained.

The outcome variable of interest was time to event for in-hospital death, which was estimated with Time 0 ($t_\#$), which corresponds to the date of the first PP, and time 1 ($t_\$$),as the date of decannulation, indicating either the success of the therapy or the death of the patient.

Data analysis

Quantitative variables were expressed with measures of central tendency (mean) and dispersion (standard deviation), after verifying the normality of their distribution using the Shapiro–Wilk test; alternatively, they were described using medians and interquartile ranges. Categorical variables were reported using absolute and relative frequencies. To estimate intergroup statistical differences (for example, between survivors or between cycles), a two-proportion Z-test was used. In polytomous qualitative variables, expected cell frequencies were calculated; should any of them be ≤ 5, Fisher's exact test was used, and when they were > 5, the chi-square test was used (X^2) instead. In order to correct the level of significance for multiple comparisons and to maintain the type I error at 0.05, the Bonferroni method was used, when appropriate.

The in-hospital survival function for the event of interest was measured using a non- parametric model (the Kaplan–Meier estimator) by groups according to the number of PP cycles (first group for patients who received ≤ 3 cycles and the second group for those patients who received > 3 cycles). Log-rank and Wilcoxon tests were used to finddifferences between these survival curves.

A semiparametric Cox Proportional Hazards method was used to adjust this survival function for potential confounding and interaction variables, and bivariate and multivariate estimates of the association between the number of PP cycles and survival were obtained. The regressor variables were selected using the stepwise technique witha bringing in probability of 10% and a removing probability of 15%. Graphical methods such as log-log plots (–In[-survival function] versus In t) were used to evaluate the proportional hazard assumption in search of parallel curves, and Schoenfeld residuals for the overall assessment and for each of the variables included within the model (looking for the absence of slope in the graphs).

Statistical tests were considered significant at a value of $p \leq 0.05$ and, whenever pertinent, 95% confidence intervals (95% CI) were used. Data analysis was conductedusing the statistical package STATA version 15.

Results

A total of 35 patients were included in the study, 17 survived and 18 died. This corresponds to a cumulative incidence of mortality of 51.42%. Table 1 describes the sociodemographic and clinical characteristics of the patients who were pronated, overalland according to group. No significant differences were found in any of these variablesbetween individuals who survived during the hospital stay versus those who did not. Notably, the time elapsed between the ECMO initiation, and the first PP cycle was 5.7 days for all patients, 5.76 for the survivors and 5.66 for the deceased; the average number of cycles was 3.68 per patient in general, 3.94 for the group of survivors and

3.44 for the group of deceased patients, however, no significant differences could be observed (Table 1).

Additionally, a comparison of the same characteristics was performed. In this case, patients were classified by PP cycles (≤ and > 3 cycles). Table 2 shows no statistical significance in this comparison. However, gasometric and ventilatory variables were compared before and after PP. A non-significant increase in PaO_2 (61.32 mmHg vs. 64.15 mmHg, $p = 0.09$) and a non- significant decrease in PaO_2/FiO_2 (141 vs. 139, $p = 0.09$) can be observed during PP. The variables in MV did not yield significant differences in terms of PP. There was a non-significant increase in compliance (9.44 vs. 10.75 mL/cmH_2O, $p = 0.28$) and tidal volume (191 vs. 203 mL, p = *0.14*) (Table 3). The total estimated number of PP cyclesperformed on the 35 patients was 129 cycles.

Considering the average of three PP cycles per patient, these were classified into those who received ≤ 3 cycles (19 patients) and >3 cycles (16 patients). In the group with ≤ 3 cycles, no differences could be observed in gasometric or ventilatory variablesbefore and during PP. In the group who received >3 cycles PP, a significant increase in the values is reflected during the PP of PaO_2 (60.13 vs. 66.15, $p = 0.0065$) and of PaO_2/FiO_2 (136 vs. 155, $p = 0.0026$). When comparing values before PP in this samegroup, the variables in MV showed a non-significant increase in the tidal volume during PP (192.90 vs. 212.75, $p = 0.07$), as wellas in terms of lung compliance (10.29 vs. 13.03, $p = 0.46$) (Table 4).

In-hospital survival estimation via Kaplan–Meier showed differences, although these differences were statistically nonsignificant, for the group with >3 cycles PP ($p = 0.072$) (Figure 1 and Table 5). A crude estimate showed no association between the number ofcycles and survival; however, when using a multivariate method to adjust for confoundingvariables, PP in more than 3 cycles reduces mortality risk by 80% compared with subjectswho underwent ≤ 3 PP cycles (hazard ratio: 0.200, CI 95%: 0.0517–0.7800, p = *0.020)* (Table 6). This model showed an adequate fit and compliance with the assumption of proportional risks (Figure 2).

Table 1 Sociodemographic and clinical characteristics of patients pronated during ECMO according to in-hospital survival outcome, period 2020–2021

Variables	Consolidated N = 35	In-hospital survival		
Age		Yes n = 17	No n = 18	p value
Mean (SD)	38.91 (9.30)	36.11 (8.77)	41.55 (9.24)	0.0839*
Sex				
Man	29–82.86	13–76.47	16–88.88	0.3299**
BMI				
Median (IQR)	29.05 (25.71–33.56)	28.08 (26.98–33.56)	29.76 (25.71–31.93)	0.7664***
RESP Score				
Mean (SD)	3.17 (1.33)	3.11 (1.21)	3.22 (1.47)	0.8213*
MV days prior to ECMO support				
Mean (SD)	4.51 (2.69)	4.05 (2.22)	4.94 (3.07)	0.3385*
Days between ECMO support initiation and first PP cycle during ECMO				
Mean (SD)	5.71 (3.48)	5.76 (3.66)	5.66 (3.41)	0.9352*
Number of PP cycles during ECMO				
Mean (SD)	3.68 (2.47)	3.94 (2.79)	3.44 (2.17)	0.5600*

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; RESP, Respiratory ECMO Survival Prediction; MV, mechanical ventilation.

*Differences calculated using Z-test for difference of means.

**Differences calculated using Z-test for differences of proportions.

***Differences calculated by Wilcoxon rank sum.

Table 2 Sociodemographic and clinical characteristics of patients pronated during ECMO according to the number of PP cycles, period 2020–2021

Variables	Consolidated n = 35	PP cycles		
		≤3 cycles n = 19	>3 cycles n = 16	p value
Age				
Mean (SD)	38.91 (9.30)	39.26 (8.59)	38.5 (10.36)	0.8131*
Sex				
Man	29–82.86	16–84.21	13–81.25	0.4741**
BMI				
Mean (SD)	29.89 (5.04)	29.74 (4.23)	30.08 (6.00)	0.8432 *
RESP Score				
Mean (SD)	3.17 (1.33)	3.26 (1.32)	3.06 (1.38)	0.6654*
MV days prior to ECMO support				
Mean (SD)	4.51 (2.69)	4.47 (2.71)	4.56 (2.75)	0.9243*
Days between ECMO support initiation and first PP cycle during ECMO				
Median (IQR)	5 (2–9)	6 (4 –9)	3.5 (2–9)	0.1764***

Abbreviations: SD, standard deviation; BMI, body mass index; IQR, interquartile range; RESP, Respiratory ECMO Survival Prediction; MV, mechanical ventilation.

*Differences calculated using Z-test for difference of means.

** Differences calculated using Z-test for o differences of proportions.

***Differences calculated by Wilcoxon rank sum.

Table 3 Arterial blood gases and mechanical ventilation before and after a PP cycle in patients with ECMO support

Variables n = 35	Pre-pronation	Post pronation	p value
Arterial gases			
pH			
Mean (SD)	7.42 (0.03)	7.42 (0.04)	0.9688*
PaO2			
Mean (SD)	61.32 (7.68)	64.15 (11.13)	0.0997*
PCO2			
Median (IQR)	38 (35.97–42.9)	38.4 (35.91–41.4)	0.9543**
PaO2/FiO2			
Median (IQR)	141 (114–174)	139.6 (118.25–191)	0.0948**
Mechanical ventilation			
Breathing rate			

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Table 3 Continued...

Variables n = 35	Pre-pronation	Post pronation	p value
Mean (SD)	11.69 (1.36)	11.69 (1.30)	0.9786*
PEEP			
Mean (SD)	10.87 (1.28)	10.98 (1.31)	0.3133*
Peak pressure †			
Median (IQR)	30.29 (29.86–32.4)	30.58 (29.14–32.5)	0.6139**
Plateau pressure †			
Median (IQR)	29.78 (28.5–32)	29.87 (28–32.25)	0.6041**
Driving pressure †			
Mean (SD)	18.93 (2.75)	18.75 (3.33)	0.7346*
Control pressure †			
Median (IQR)	20 (18.21–20.5)	18.76 (18–20)	0.2517**
Flow			
Mean (SD)	5.61 (0.72)	5.65 (0.57)	0.5652*
Compliance †			
Median (IQR)	9.44 (6.04–13.47)	10.75 (7.01–14.7)	0.2895**
Tidal volume †			
Mean (SD)	191.19 (77.71)	203.37 (85.40)	0.1466*

*Differences calculated using Z-test for difference of means for dependent samples.

**Differences calculated with Wilcoxon rank sum test for dependent samples.

† Variable not available for all subjects

Table 4 Arterial gases and mechanical ventilation based on PP cycles

	≤ 3 cycles (n = 19)			> 3 cycles (n = 16)		
Variables	**Pre-pronation**	**Post pronation**	**P value**	**Pre-pronation**	**Post pronation**	**p value**
pH						
Mean (SD)	7.42 (0.03)	7.41 (0.05)	1.000*	7.42 (0.03)	7.43 (0.02)	1.000*
PaO2						
Mean (SD)	62.31 (9.25)	62.46 (13.66)	1.000*	60.13 (5.33)	66.15 (6.98)	0.0065*
PCO2						
Mean (SD)	39.73 (6.23)	40.14 (7.23)	1.000*	38.97 (3.97)	38.31 (2.25)	1.000*
PaO2/FiO2						
Mean (SD)	154.18 (52.60)	152.98 (66.41)	1.000*	136.01 (31.92)	155.69 (32.84)	0.0026*
Breathing rate						
Mean (SD)	11.71 (1.53)	11.64 (1.41)	1.000*	11.66 (1.18)	11.74 (1.21)	1.000*
PEEP						
Mean (SD)	10.92 (1.31)	11.07 (1.37)	1.000*	10.81 (1.28)	10.88 (1.28)	1.000*
Peak pressure						
Median (IQR)	30.5 (30–34)	31.5 (30–33) †	1.000**	30.14 (28.87–31.15)	30.06 (28.28–31.6)	1.000**
Plateau pressure						
Median (IQR)	30.83 (28.67–33) †	30.58 (29.33–32.5)†	1.000**	29.43 (26.05–30.19)	28.71 (26.78–30)	1.000**
P. driving						
Mean (SD)	20.09 (3.0) †	19.73 (3.42) †	1.000*	18.08 (2.61)	17.79 (2.93)	1.000*
Control pressure						
Median (IQR)	20 (18.67–22) †	20 (18–20) †	1.000**	18.67 (18–20) †	18.5 (18–20) †	1.000**
Flow						
Mean (SD)	5.36 (0.77)	5.50 (0.63)	1.000*	5.91 (0.55)	5.83 (0.46)	1.000*
Compliance						
Median (IQR)	8.76 (4.52–12.79) †	7.97 (6.25–14.3) †	1.000**	10.29 (7.19–14.95)	13.03 (9.58 –15.83)†	0.4628**
Tidal volume						
Mean (SD)	189.57 (95.14) †	200.39 (105.33) †	1.000*	192.90 (56.76)	212.75 (59.18)	0.0715*

Abbreviations: SD, standard deviation; IQR, interquartile range; MV, mechanical ventilation.

*Differences calculated using Z-test for difference of means for dependent samples.

**Differences calculated by Wilcoxon rank sum test for dependent samples.

*** p -value adjusted for Bonferroni correction using $pi = m(1, p * 13), i = 1,2, \ldots .,13$.

† Variable not available for all subjects.

Table 5 Estimation of in-hospital survival using the Kaplan– Meier method

Time & (days)	$S(t)$	
	≤3 cycles	>3 cycles
2	0.9474	1
11	0.6998	0.9333
20	0.4798	0.7778
29	0.4798	0.5926
38	0.1599	0.4741
47	-	0.3556
56	-	0.3556
65	-	0.3556
74	-	0.3556
83	-	-

Abbreviations: (t): survival function calculated using the Kaplan–Meier method.

Table 6 Association between the number of PP cycles and in- hospital survival in pronated patients during ECMO, period 2020– 2021

Variable	In-hospital survival		HR	CI 95% HR	P-value	HR*	CI 95% HR	P-value
	Yes	No						
≤ 3 cycles	9–52.94%	10–55.56	1	-	-	1	-	-
> 3 cycles	8–47.06	8–44.44	0,395	0.138–1.129	0,083	0,200	0.0517–0.780	0.02

*Adjusted for the variables: age, days elapsed from ECMO initiation to first PP cycle and RESP Score.

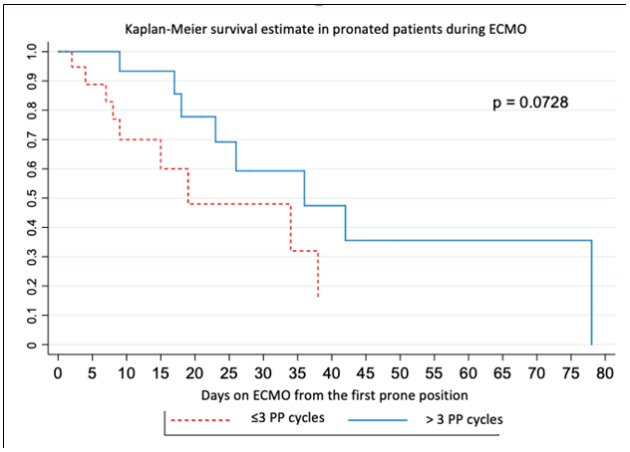

Figure 1 Kaplan-Meier survival estimate in pronated patients during ECMO.

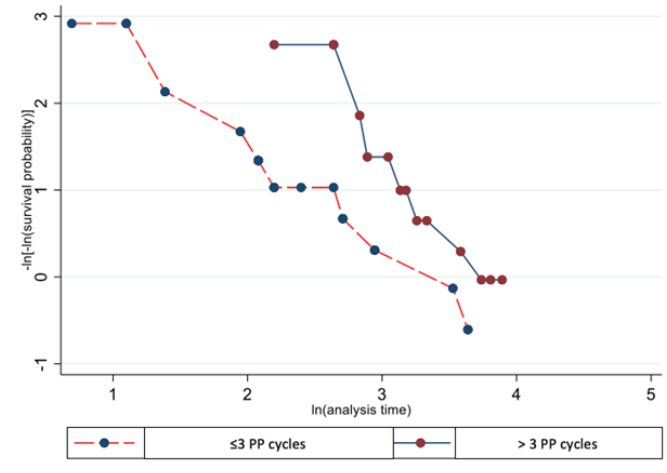

Figure 2 Evaluation of the proportional hazards assumption of the multivariatemodel in Table 6.

Discussion

Evidence regarding PP in patients with ECMO support has increased over time. Several studies, mostly retrospective cohort studies, have reported improved oxygenation and respiratory compliance with a concomitant decrease in CO_2, especially in patients with a high BMI and whose etiology was viral pneumonia. Severe hypoxemia (PaO_2/FiO_2 < 85),a plateau pressure > 32 cmH_2O, and ECMO weaning failure after 7–10 days of support, were among the PP indications.[5]

Our retrospective cohort of 35 patients with severe hypoxemia on ECMO placed on PP represented a 28.92% of the total number of patients (121 patients on ECMO for SARS-CoV-2 in the period 2020–2021) with a slightly lower survival, possibly attributable to the greatest pulmonary compromise. Among those patients who were in PP, there were no major complications associated with this procedure, and a significant improvement in oxygenation and a tendency toward improvement in ventilatory mechanics could be observed in those patients undergoing more than three PP cycles.

The most representative multicenter study included six centers specialized in ECMO and240 patients, of which, 107 were managed with PP for 15 hours on average, suffering minor and reversible complications in 6% of cases. An improvement in oxygenation could be observed and, despite a longer duration on ECMO (16 vs. 10 days), a lower hospital mortality was observed in the PP group on ECMO (30% vs. 53%, $p = 0.0241$).[6]

The use of ECMO support in patients with ARDS induced by SARS-CoV-2 has increased,and owing to the severe pulmonary compromise, refractory hypoxemia under this supporthas also increased. Within the clinical approach, PP in a retrospective study was considered in 56% of ECMO cases with severe hypoxemia (PaO_2/FiO_2 < 80 mmHg) despite FiO_2 and FDO_2 of 100%, and in cases of extensive pulmonary consolidation on chest images (>50% of the lung volume). Oxygenation improved without changes neither in CO_2 nor in lung compliance, and with an increase in mortality in the PP group (78.6% vs. 27.3%) explained by the greater severity and extent of the

pulmonary consolidation, as well as through the possible exposure to greater mechanical power.[7]

In the present study, PP for >3 cycles was a protective factor for survival. A possible explanation for the clinical and survival improvement with prolonged PP cycles may be the slow alveolar recruitment process that occurs with position change in patients with severely compromised lung compliance.

A recent meta-analysis consolidated data from 13 studies as follows: 12 observational studies, 4 of them with match control. PP was started after ECMO initiation with a total of1836 patients. The reason specified for PP only in a few studies was severe hypoxemia.PP had a prolonged duration of >12 hours with an average 2–3 sessions. PP was associated with a significant improvement in survival at 28 days (74% vs. 58%; RR 1.31with 95% CI of 1.21–1.41; $p < 0.001$). Hospital mortality in the ICU at 60 and 90 days alsoimproved. Conversely, the duration of MV increased in prone patients by 11.38 days on average. There were no major complications reported in any of the studies.[8]

Among the strengths of our study, we not only assessed PP but also examined the impactof PP based on the number of cycles, regardless of the initial results in oxygenation andventilatory mechanics. These outcomes proved a reduction in mortality in patients who received >3 PP cycles.

Our study has some limitations. The time variable from VV ECMO initiation and PP mayhave influenced the results, which in our study began approximately 5.7 days from VV ECMO initiation. This time may be late when compared with other studies that have shown benefits in the survival rates.

Finally, the sample size in our study was limited to prove an absolute reduction in the riskof mortality. Although a benefit in the survival rates of those patients with refractory hypoxemia on VV ECMO who received >3 PP cycles could be demonstrated, further studies with larger samples to improve the level of evidence would be necessary to confirm these results.

Conclusion

The benefits of VV ECMO support against ARDS lead to an increase in cases, andconsequently, to a proportional increase in more severe cases of hypoxemia, evenwhen patients are on VV ECMO. PP is a strategy that improves the parameters of mechanical ventilation, oxygenation, and survival. The duration and number of PP cycles is a relevant variable to consider when deciding to start PP in patients with severe hypoxemia on VV ECMO.

Acknowledgments

None.

Conflicts of interest

None.

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