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ORIGINAL

Associations between ventilator settings during extracorporeal membrane oxygenation for refractory hypoxemia and outcome in patients with acute respiratory distress syndrome: a pooled individual patient data analysis

Mechanical ventilation during ECMO

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Abstract

Purpose: Extracorporeal membrane oxygenation (ECMO) is a rescue therapy for patients with acute respiratory distress syndrome (ARDS). The aim of this study was to evaluate associations between ventilatory settings during ECMO for refractory hypoxemia and outcome in ARDS patients.

Methods: In this individual patient data meta-analysis of observational studies in adult ARDS patients receiving ECMO for refractory hypoxemia, a time-dependent frailty model was used to determine which ventilator settings in the first 3 days of ECMO had an independent association with in-hospital mortality.

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Take-home message: "Maintenance of a low driving pressure during the first days of ECMO in patients with acute respiratory distress syndrome is associated with reduced mortality".

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Results: Nine studies including 545 patients were included. Initiation of ECMO was accompanied by significant decreases in tidal volume size, positive end-expiratory pressure (PEEP), plateau pressure, and driving pressure (plateau pressure − PEEP) levels, and respiratory rate and minute ventilation, and resulted in higher PaO_2/FiO_2, higher arterial pH and lower $PaCO_2$ levels. Higher age, male gender and lower body mass index were independently associated with mortality. Driving pressure was the only ventilatory parameter during ECMO that showed an independent association with in-hospital mortality [adjusted HR, 1.06 (95 % CI, 1.03–1.10)].

Conclusion: In this series of ARDS patients receiving ECMO for refractory hypoxemia, driving pressure during ECMO was the only ventilator setting that showed an independent association with in-hospital mortality.

Keywords: Mechanical ventilation, ARDS, Refractory hypoxemia, ECMO, PEEP, Driving pressure

Introduction

The acute respiratory distress syndrome (ARDS) is characterized by lung injury caused by either indirect or direct insults, which could be worsened by the way mechanical ventilation is applied [1]. Indeed, tidal overdistension (volutrauma) and cyclic alveolar recruitment and derecruitment (atelectrauma) during ventilation may further damage the lungs, and increase local production and release of inflammatory mediators (biotrauma), eventually resulting in multiple organ dysfunction and death [2]. So-called lung-protective ventilation strategies using low tidal volumes (6 mL/kg predicted body weight, PBW) and higher levels of positive end-expiratory pressure (PEEP) to prevent volutrauma, atelectrauma and biotrauma are by now widely accepted approaches in ARDS patients [3–7].

Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a rescue therapy for refractory hypoxemia in ARDS patients [8]. Initiation of ECMO allows reductions in the tidal volume size, PEEP and plateau pressure (Pplat) levels, as well as inspired oxygen fractions (FiO_2) [8–10], which all may help to improve outcome via prevention of additional lung injury [11, 12]. The impact of different ventilator settings in ARDS patients undergoing ECMO is, however, unclear. Actually, to date, there have been no studies that have addressed the relationship between ventilator settings during ECMO and outcome of ARDS patients [9–16].

To examine the hypothesis that certain ventilator settings during ECMO are associated with outcome, we performed an individual patient data meta-analysis of observational studies in ventilated ARDS patients receiving ECMO for refractory hypoxemia, and determined which ventilator settings have an independent association with in-hospital mortality.

Methods

Setting and patients

We identified eligible studies by a blind electronic search by two authors of MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Register of Controlled Trials (CENTRAL) up to January 2016. All investigations describing ventilation practice in adult ARDS patients undergoing ECMO for refractory hypoxemia were considered for inclusion. All reviewed articles and cross-referenced studies from these articles were screened for pertinent information, and were assessed for evidence of quality using the Newcastle Ottawa Scale for observational studies.

Data collection

After exclusion of duplicate patients from the retrieved databases, the following variables were assessed for each patient: (1) demographic data, (2) interval between initiation of ventilation and start of ECMO, (3) ECMO settings and complications, (4) ventilation settings and blood gas analysis parameters before and daily after initiation of ECMO, (5) laboratory and vital signs, and (6) in-hospital mortality. All settings, parameters and signs were collected once daily at a fixed moment in the morning as per protocols of the original studies.

Definitions

Driving pressure (ΔP) was calculated as inspiratory Pplat minus the PEEP level (as measured in the ventilator). PaO_2/FiO_2 was calculated using the patient's PaO_2 and the FiO_2 set at the ventilator.

Outcome

The primary outcome was in-hospital mortality.

Analysis plan

As a first step, ventilator settings and other parameters before and after initiation of ECMO were described and compared. The time between the start of mechanical ventilation and ECMO was categorized according to tertiles. Then, the associations between ventilator settings during ECMO and outcome were analyzed.

Statistical analysis

Normally distributed data were described as mean ± standard deviation while non-normally distributed data were described as median [quartile range (QR = 25–75 %)]. Categorical variables were described as proportions (%) [17]. Continuous variables were compared using Student's *t* tests or analysis of variance *or* Mann–Whitney tests or Kruskal–Wallis tests according to the distribution of the variables. Categorical variables were compared using Chi-squared or Fisher's exact tests. Line graphs were used to show ventilatory settings and parameters during the first 3 days of ECMO.

Multiple imputation was conducted to deal with missing values in the retrieved database. For this imputation, the following variables were included: age, gender, BMI, risk of death, Sequential Organ Failure Assessment score (SOFA), chronic obstructive pulmonary disease (COPD), diabetes mellitus, Influenza H_1N_1 infection, time between start of mechanical ventilation and ECMO, tidal volume (in ml/kg PBW), PEEP, Pplat, peak pressure (Ppeak), and ΔP levels, respiratory rate, FiO_2 (as set on the ventilator), minute ventilation, static compliance, $PaCO_2$, pH, PaO_2/FiO_2, duration of mechanical ventilation and ECMO, ICU and hospital length of stay, mortality, and time until mortality. Multiple imputation was conducted using the method of predictive mean matching and ten databases were created. All the models were constructed using the databases after multiple imputation.

A multivariable model was built to quantify the association between predefined ventilation parameters and mortality, while controlling for other known risk factors. We conducted multi-level analyses to adjust for clustering of the data. Therefore, a frailty model was used to determine predictors of mortality by modeling it as the dependent variable. Independent variables were selected according to biologic plausibility, and when the univariate analysis *p* value was <0.2. Then, a multivariable time-dependent frailty model [presented as hazard ratio and 95 % CI (HR and 95 % CI)] considering ΔP, FiO_2, PaO_2/FiO_2, lactate and norepinephrine as time-dependent variables was built, with study treated as random effect. Only values from the first 3 days of ECMO were considered in this model. The cluster effects induced by the structure of the data were taken into account through random effects. In the multivariable model, statistical significance was set at $p < 0.05$.

Since static compliance, Pplat level and Δ*P* showed high collinearity (Appendix Table 1, Appendix Fig. 1 in the Online Supplement), we chose to include only ΔP in the model. ΔP was chosen since recent studies and one individual patient data meta-analysis have suggested that the ΔP is the ventilatory parameter that best stratifies risk of death in ARDS patients receiving mechanical ventilation [7, 9, 18, 19]. As arterial pH and lactate levels also showed a high collinearity, we chose to include only lactate levels in the principal final model because lactate is more clinical relevant and associated with shock reversal [20, 21].

We conducted one post hoc analysis replacing ΔP by Pplat level to assess the additional impact of the later ventilatory parameter. In addition, we conducted another post hoc model including PEEP, Pplat and ΔP levels. We compared these three models (i.e., the model with the ΔP vs. the model with the Pplat levels) and assessed the fit of each model. To assess the possible relationship between the ventilatory parameters of interest (PEEP, Pplat and ΔP levels) and mortality, we conducted several mediation analyses (details of the mediation analysis are described in the Online Supplement).

All analyses were conducted with SPSS v.20 (IBM SPSS Statistics for Windows, v.20.0; IBM, Armonk, NY, USA) and R v.2.12.0 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, two-sided $p < 0.05$ was considered significant.

Results

Cohort analyzed

Sixty-one observational studies were evaluated for extraction of individual patient data. Fifty-two were not included for the following reasons: unable to send the individual patient data due to rejection or other reasons ($n = 16$); unable to establish contact with the authors ($n = 15$); ECMO provided for other indications than ARDS ($n = 8$); same cohort previously described ($n = 5$); and others ($n = 8$) (Appendix Fig. 2, Appendix Table 2 in the Online Supplement). Data from the remaining nine investigations were included and a total of 545 patients were pooled [9, 22–29]. The characteristics of the included studies are shown in Appendix Tables 3 and 4 in the Online Supplement.

Baseline characteristics

Patient characteristics are shown in Table 1. Pneumonia and pulmonary ARDS were the main diagnoses. Non-survivors were older, had lower body weight and body mass index, a higher risk of dying and higher SOFA scores. Median time from start of ventilation until initiation of ECMO was 48 (24–120) h; the difference in the median time from start of ventilation until initiation of ECMO between survivors and non-survivors was not statistically significant [48 (24–120) vs. 72 (24–144) h; $p = 0.061$) (Table 1).

Ventilatory parameters before and after initiation of ECMO

Table 1 shows ventilatory parameters before ECMO; Appendix Fig. 3 in the Online Supplement shows the distribution of modes of ventilation. The number of patients under ECMO and on ventilation on each follow-up day is shown in Fig. 1. Initiation of ECMO was accompanied by significant decreases in tidal volume size, PEEP and Pplat levels, ΔP, respiratory rate and minute ventilation (all $p < 0.001$) (Table 2; Fig. 2). Also, significant increases in PaO_2/FiO_2 and arterial pH, and decreases in $PaCO_2$ levels were noted (all $p < 0.001$) (Table 2; Fig. 3).

Outcomes

In-hospital mortality of the present cohort was 35.2 %. A cumulative incidence curve of in-hospital mortality is shown in Fig. 1. Incidence of bleeding events including intracerebral haemorrhage was higher in non-survivors (34.9 vs. 19.5 %; $p = 0.019$ and 6.2 vs. 0.8 %; $p < 0.001$) (Table 2). Duration of ECMO, mechanical ventilation, ICU and hospital length of stay in survivors were 10 (6–15) days, 25 (15–39) days, 30 (18–46) days, and 38 (26–64) days, respectively.

In the first day of ECMO, compared to survivors, the non-survivors received ventilation with higher ΔP ($p = 0.048$) and higher FiO_2 set at the ventilator ($p = 0.005$), and had lower PaO_2/FiO_2 ($p = 0.051$), lower arterial pH ($p < 0.001$) and higher lactate levels ($p = 0.003$) (Table 2).

Association between ventilator settings and mortality

Univariable analysis of factors associated with in-hospital mortality is provided in Appendix Table 5 in the Online Supplement. After adjusting for confounders, independent predictors of in-hospital mortality included a higher age, male gender, a lower body mass index, and higher lactate levels (Table 3). The only ventilatory parameter during ECMO that showed an independent association with in-hospital mortality was a higher ΔP (Table 3).

Post hoc analyses

Replacing ΔP by Pplat levels, higher age, male gender, lower BMI, higher lactate, lower PEEP and higher Pplat levels independently associated with in-hospital mortality (Appendix Table 6 in the Online Supplement). Including Pplat, PEEP and ΔP in the model, no parameter remained associated with in-hospital mortality. The comparison of the models is shown in Appendix Table 7 in the Online Supplement. Since the higher FiO_2 observed in non-survivors from ECMO might be the consequence of a too-low ECMO blood flow, we constructed a scatterplot to assess the blood flow used in survivors and non-survivors. These showed no differences between survivors and non-survivors (Appendix Fig. 4 in Online Supplement).

Mediation analyses

The results of the mediation analyses are shown in the Online Supplement Figs. 5, 6, 7, 8, 9 and 10. In the models with ΔP as the independent variable, its effect on mortality was not mediated by the PEEP level (Appendix Fig. 5 in the Online Supplement), the Pplat level (Appendix Fig. 6 in the Online Supplement) or compliance (Appendix Fig. 7 in the Online Supplement). In the models with ΔP as the mediator, the impact of the PEEP level (Appendix Fig. 8 in the Online Supplement), the Pplateau level (model 5, Appendix Fig. 9 in the Online Supplement) and compliance (model 6, Appendix Fig. 10 in the Online Supplement) was fully mediated by ΔP.

Discussion

With ECMO, it is possible to 'rest' the lungs by using lower tidal volumes, lower airway pressures, and lower FiO_2, thereby decreasing the iatrogenic consequences of mechanical ventilation [8]. There are several systematic reviews and metaanalysis of mechanical ventilation settings in patients under ECMO [10, 30–33]. The present study analyzing the largest cohort of ARDS patients under ECMO for refractory hypoxemia allowed the assessing of the associations between ventilatory settings and parameters and outcome. The results of this analysis using individual patient data suggest that the ΔP is the ventilatory parameter that best stratifies risk of death in ARDS patients receiving ECMO for refractory hypoxemia.

We grouped patients from several centers across the world, increasing the external validity of the study. Ventilatory parameters influencing mortality were identified; these may prove helpful for physicians to improve ventilator settings in patients under ECMO. A strong point of the present study is the use of multiple imputation of missing values, a technique that is designed to increase the power of the analysis and produce models that are more statistically reliable and applicable within clinical practice.

The main finding that a higher ΔP during ECMO is associated with worse survival is consistent with studies in patients with ARDS, both those conventionally treated

Table 1 Baseline characteristics of the patients and ventilatory parameters before ECMO

	All ($n = 545$)	Survivors ($n = 353$)	Non-survivors ($n = 192$)	p value[a]
Age, years	41.4 ± 14.0	39.7 ± 13.9	44.8 ± 13.6	<0.001
Gender, male	331 (60.7)	205 (58.1)	126 (67.2)	0.030
BMI, kg/m^2	29.6 ± 8.5	30.5 ± 9.0	28.1 ± 7.5	0.004
Actual weight, kg	86.6 ± 26.0	88.5 ± 27.3	83.5 ± 23.4	0.036
PBW, kg	65.0 ± 9.7	64.6 ± 10.1	65.5 ± 8.7	0.331
Risk of death, %[b]	40.4 ± 25.9	37.6 ± 24.6	46.0 ± 27.6	0.001
SOFA	10.7 ± 4.3	10.2 ± 4.0	11.6 ± 4.8	0.002
LIS	3.5 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	0.753
Co-morbidities				
COPD	60 (11.0)	36 (10.3)	24 (12.5)	0.835
Diabetes	42 (7.7)	25 (7.1)	17 (8.8)	0.644
Hypertension	42 (7.7)	24 (6.9)	18 (9.4)	0.407
CAD	2 (0.4)	1 (0.3)	1 (0.5)	0.926
HIV	2 (0.4)	0 (0.0)	2 (1.0)	0.252
H_1N_1	264 (48.5)	168 (48.0)	96 (50.0)	0.575
Time between MV-ECMO, h	48.0 (24.0–120.0)	48.0 (24.0–120.0)	72.0 (24.0–144.0)	0.061
≤24 h	228 (41.8)	157 (44.5)	71 (37.0)	
24–72 h	110 (20.2)	78 (22.1)	30 (15.6)	0.006
>72 h	207 (38.0)	118 (33.4)	91 (47.4)	
Indication of ECMO				
Refractory hypoxemia	526 (96.5)	340 (97.1)	186 (96.9)	0.247
Hypercapnia	19 (3.5)	10 (2.9)	9 (3.1)	
Severity of ARDS				
Mild	3 (0.6)	2 (0.3)	1 (0.5)	0.544
Moderate	52 (9.6)	37 (10.6)	15 (7.9)	
Severe	490 (89.9)	314 (89.1)	176 (91.6)	
Type of ARDS				
Pulmonary	501 (92.4)	325 (92.1)	176 (91.7)	0.812
Non-pulmonary	44 (7.6)	28 (7.9)	16 (8.3)	
Cause of ARDS				
Pneumonia	454 (83.8)	295 (84.2)	159 (82.8)	0.790
Non-pulmonary sepsis	13 (1.8)	9 (1.7)	4 (2.1)	
Trauma	48 (8.9)	32 (9.2)	16 (8.3)	
Other	30 (5.5)	17 (4.9)	13 (6.8)	
Mode of ventilation				
Pressure-controlled	273 (50.1)	188 (53.2)	85 (44.2)	0.116
Volume-controlled	107 (19.6)	57 (16.2)	48 (24.9)	
SIMV	59 (10.8)	32 (9.3)	27 (14.0)	
Pressure support	1 (0.2)	1 (0.5)	0 (0.0)	
HFPV	85 (15.6)	61 (17.1)	24 (12.4)	
APRV	12 (2.2)	4 (1.4)	8 (4.2)	
Other	8 (1.5)	7 (2.3)	1 (0.3)	
Ventilatory parameters				
Tidal volume, ml/kg PBW	6.0 ± 1.9	6.2 ± 1.8	5.8 ± 2.1	0.032
Tidal volume, ml/kg ABW	4.8 ± 1.8	4.8 ± 1.8	4.9 ± 1.8	0.840
PEEP, cmH_2O	13.7 ± 4.3	13.7 ± 4.0	13.6 ± 5.0	0.733
FiO_2, %	0.90 ± 0.17	0.91 ± 0.17	0.91 ± 0.16	0.944
Plateau pressure, cmH_2O	31.1 ± 5.7	30.7 ± 5.2	32.2 ± 6.3	0.032
Driving pressure, cmH_2O	17.7 ± 6.8	16.9 ± 6.4	19.4 ± 7.3	0.004

Table 1 continued

	All ($n = 545$)	Survivors ($n = 353$)	Non-survivors ($n = 192$)	p value[a]
Respiratory rate, bpm	21.9 ± 7.9	21.2 ± 6.9	23.2 ± 9.4	0.012
Minute ventilation, l/min	9.1 ± 3.9	9.0 ± 3.7	9.2 ± 4.2	0.644
Static compliance[c]	26.8 ± 16.9	27.7 ± 17.6	24.8 ± 15.2	0.178
Laboratory parameters				
PaO_2, mmHg	64.8 ± 21.2	64.4 ± 23.2	65.2 ± 20.2	0.715
PaO_2/FiO_2, mmHg	72.6 ± 38.5	73.2 ± 38.6	71.3 ± 39.0	0.610
$PaCO_2$, mmHg	58.3 ± 22.7	57.3 ± 22.1	60.3 ± 23.8	0.206
pHa	7.27 ± 0.15	7.29 ± 0.14	7.24 ± 0.16	0.008
Lactate, mg/dL	33.5 ± 36.4	29.4 ± 23.6	42.1 ± 42.1	0.031
Hemodynamics				
MAP, mmHg	70.8 ± 15.5	71.5 ± 16.4	71.3 ± 14.9	0.979
Norepinephrine, µg/kg/min[d]	0.40 ± 1.29	0.32 ± 0.89	0.54 ± 1.90	0.258

Data shown as mean ± standard deviation, number (percentage) or median (interquartile range)

ECMO extracorporeal membrane oxygenation, *BMI* body mass index, *PBW* predicted body weight, *SOFA* sequential organ failure assessment, *COPD* chronic obstructive pulmonary disease, *CAD* coronary artery disease, *HIV* human immunodeficiency virus, H_1N_1 influenza A virus subtype H_1N_1, *LIS* lung injury score, *MV* mechanical ventilation, *ARDS* acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, *BPM* breaths per minute, *SIMV* synchronized intermittent mandatory ventilation, *HFPV* high-frequency percussive ventilation, *APRV* airway pressure release ventilation, *ABW* actual body weight, *MIN* minutes, FiO_2 inspired fraction of oxygen

[a] p for survivor vs. no-survivor

[b] Predicted by APACHE II, APACHE III, SAPS II or SAPS III

[c] Static compliance calculated as tidal volume/plateau pressure minus PEEP (ml/cmH_2O)

[d] Defined as total dose during whole day divided by weight and 1440 min

[7, 18, 19] and those receiving ECMO [9, 29]. The results of the present analysis builds upon the results of several preclinical studies in animals showing that cell and tissue damage is more closely related to the amplitude of cyclic stretch than to maximal or sustained stretch, suggesting a causal link between driving pressure and lung injury [34, 35]. A decline in ΔP after ECMO initiation was established largely by tidal volume and plateau pressure changes, as there were only small changes in PEEP settings.

The benefit of higher PEEP levels in ARDS remains controversial [5]. The Extracorporeal Life Support Organization (ELSO) guideline recommends a PEEP of 10 cmH_2O during ECMO [21]. A recent study also suggests that higher levels of PEEP during ECMO for patients with ARDS are associated with reduced mortality [9]. In the present analysis, however, higher PEEP was not associated with better outcome when included in the multivariable analysis. Recent evidence suggests that the change in ΔP resulting from an increase in PEEP levels is an important predictor of survival in patients with ARDS [7]. In other words, changes in the PEEP level could improve outcome through its effects on the ΔP: if the ΔP decreases, outcomes could improve, but when ΔP increases, outcomes could become worse.

Opposite to our findings, use of higher FiO_2 during ECMO has been found to be independently associated with a worse outcome in other studies. While it could be that the need for higher FiO_2 simply reflects disease severity, it could mean that: (1) too high FiO_2 are harmful; or (2) there was insufficient oxygenation from ECMO device, because of an insufficiently low blood flow with respect to cardiac output in some patients. Indeed, high FiO_2 may induce pulmonary injury, at least in part by increased oxidative stress via increased levels of reactive oxygen-derived free radicals, with an influx of inflammatory cells, increased permeability and endothelial cell injury [36, 37].

An important relationship between duration of ventilation prior to ECMO initiation and mortality has previously been reported [38, 39]. This was not confirmed in the present study and in another large cohort analyzing mechanical ventilation during ECMO [9]. One possible explanation is that in this cohort almost all patients received ECMO within 7 days after the start of

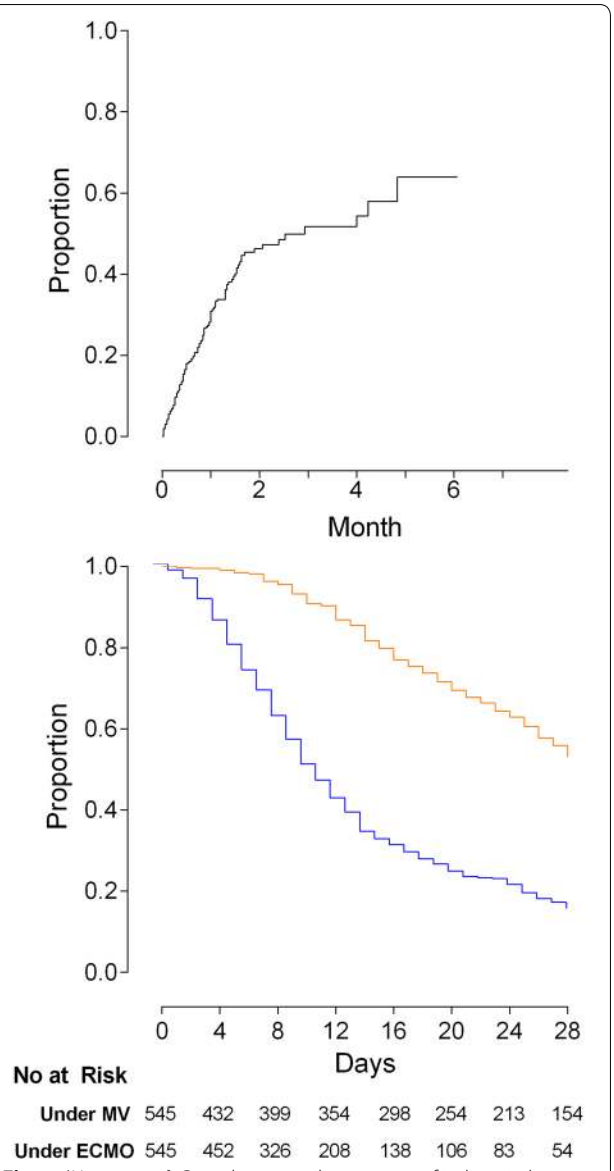

Fig. 1 (*Upper panel*) Cumulative incidence curve of in-hospital mortality; (*lower panel*) number of patients under mechanical ventilation (*orange line*), or ECMO (*blue line*)

mechanical ventilation. Also, the risk of death calculated by prognostic scores was not retained in our multivariable analysis. One possible explanation for this is that severity scores are usually calculated from data collected at ICU admission and the first day of stay in the ICU, and not at ECMO initiation. The finding that higher lactate was associated with mortality in the present cohort is similar to several reports in patients receiving ECMO for respiratory failure [20, 39] and cardiogenic shock [40].

Tidal volume size, PEEP and Pplat levels in patients before ECMO in the present study were similar to those previously reported [29]. In a recent study, higher Pplat levels were found as the only ventilatory parameter associated with mortality (of note, ΔP was not included in the model used in that study) [29]. The Predicting Death for Severe ARDS on VV-ECMO (PRESERVE) score reported Pplat levels before ECMO as one important prognostic factor for long-term mortality [20]. Finally, the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score included Ppeak levels before ECMO in its model to assess short-term mortality [41].

From a physical perspective, the process of lung injury must be related to the energy transfer from the ventilator to the lung. At each breath, the ventilator transfers some energy to the respiratory system, and there is considerable dissipation of energy, probably resulting in heat and lung tissue damage during each breath. This energy is closely related to the ΔP and respiratory rate [42]. ECMO could allow the lung to rest, through the reduction of driving pressure via tidal volume and plateau pressure reduction and/or increase of PEEP, and through the decrease in respiratory rate via increase in sweep gas flow and $PaCO_2$ removal.

Mechanical ventilators are set using diverse combinations of tidal volume sizes, airway pressures, air flows, and respiratory rates. These variables, together, could be quantified as mechanical power [43]. Recently, it was shown that lung injury is highly dependent from mechanical power, that is, the product of tidal volume size, Pplat, and respiratory rate [43]. If mechanical power is 'excessive', then the chemical bonds of the polymers composing the extracellular matrix could get disrupted [43]. The relationship between mechanical power and outcomes in patients undergoing ECMO needs further attention in future studies.

The present analysis has several limitations, including its non-randomized design, which precludes any inference of causality regarding the association between ΔP and outcome. In addition, it cannot be excluded that residual confounding not accounted for in this study might have biased the results. Also, ventilatory settings and parameters were collected only once per day in the original studies. Mechanical ventilation, however, is a continuous and dynamic intervention, and settings may have changed rapidly with a 24-h period, especially

Table 2 Parameters in the first day of ECMO and complications

	All ($n = 545$)	Survivors ($n = 353$)	Non-survivors ($n = 192$)	p value[a]
Ventilatory parameters				
Tidal volume, ml/kg PBW	4.0 ± 1.7	4.0 ± 1.6	4.0 ± 1.9	0.934
Tidal volume, ml/kg ABW	3.2 ± 1.6	3.1 ± 1.5	3.4 ± 1.8	0.075
PEEP, cmH_2O	12.9 ± 3.4	13.0 ± 3.3	12.5 ± 3.7	0.125
FiO_2	0.69 ± 0.24	0.67 ± 0.23	0.74 ± 0.23	0.005
Plateau pressure, cmH_2O	26.2 ± 4.6	26.0 ± 4.3	26.7 ± 5.1	0.205
Driving pressure, cmH_2O	13.7 ± 5.3	13.3 ± 4.8	14.5 ± 6.2	0.048
Respiratory rate, bpm	17.8 ± 8.0	17.4 ± 7.7	18.7 ± 8.7	0.105
Minute ventilation, l/min	5.0 ± 3.2	4.8 ± 2.9	5.3 ± 3.3	0.117
Static compliance[b]	23.2 ± 18.8	22.7 ± 16.9	24.1 ± 22.3	0.564
Laboratory parameters				
PaO_2, mmHg	95.9 ± 55.9	96.8 ± 51.6	94.6 ± 64.9	0.702
PaO_2/FiO_2, mmHg	152.5 ± 96.8	158.3 ± 96.8	139.1 ± 95.9	0.051
$PaCO_2$, mmHg	40.3 ± 9.5	40.1 ± 9.2	40.4 ± 9.7	0.764
pHa	7.39 ± 0.11	7.41 ± 0.08	7.36 ± 0.14	<0.001
Lactate, mg/dL	34.8 ± 38.1	29.9 ± 34.8	46.7 ± 43.0	0.003
ECMO parameters				
Flow, l/min	4.3 ± 1.1	4.3 ± 1.1	4.4 ± 1.1	0.482
Sweep gas flow, l/min	6.2 ± 2.3	6.1 ± 2.1	6.4 ± 2.6	0.459
Hemodynamics				
MAP, mmHg				
Day 01	75.8 ± 10.7	76.0 ± 9.5	71.4 ± 13.8	0.420
Day 02	78.3 ± 12.7	78.8 ± 12.4	79.7 ± 16.9	0.496
Day 03	80.7 ± 8.3	81.4 ± 8.5	78.0 ± 9.5	0.750
Norepinephrine, µg/kg/min[c]				
Day 01	0.12 ± 0.39	0.11 ± 0.29	0.15 ± 0.55	0.377
Day 02	0.07 ± 0.30	0.07 ± 0.18	0.10 ± 0.48	0.915
Day 03	0.06 ± 0.25	0.06 ± 0.20	0.07 ± 0.34	0.535
Complications				
Bleeding events	136 (24.9)	69 (19.5)	67 (34.9)	0.019
Intracerebral hemorrhage	15 (2.8)	3 (0.8)	12 (6.2)	<0.001

Data shown as mean ± standard deviation or number (percentage)

ECMO extracorporeal membrane oxygenation, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *BPM* breaths per minute, *ABW* actual body weight, *MIN* minutes, FiO_2 inspired fraction of oxygen

[a] p for survivor vs. no-survivor

[b] Static compliance calculated as tidal volume/plateau pressure minus PEEP (ml/cmH_2O)

[c] Defined as total dose during whole day divided by weight and 1440 min

shortly after the start of ECMO. Data from only the first 3 days of ECMO were included in the analysis of mortality because recent studies have suggested that ventilation during such a period is the most important factor related to the prognosis of patients [9, 33]. Whether specific ventilatory strategies after day 3 would change patient outcomes is yet to be determined, and larger prospective studies may shed light onto this aspect. Also, the fact that ΔP could represent only a marker of disease severity should be taken in account. It was impossible to determine the number of patients with severe sepsis or septic shock, and the potential impact of this condition in the outcome was not assessed. However, since most of the patients presented with pneumonia and use of vasoactive drugs, one could assume that most of them had severe sepsis and septic shock. The heterogeneity of the different

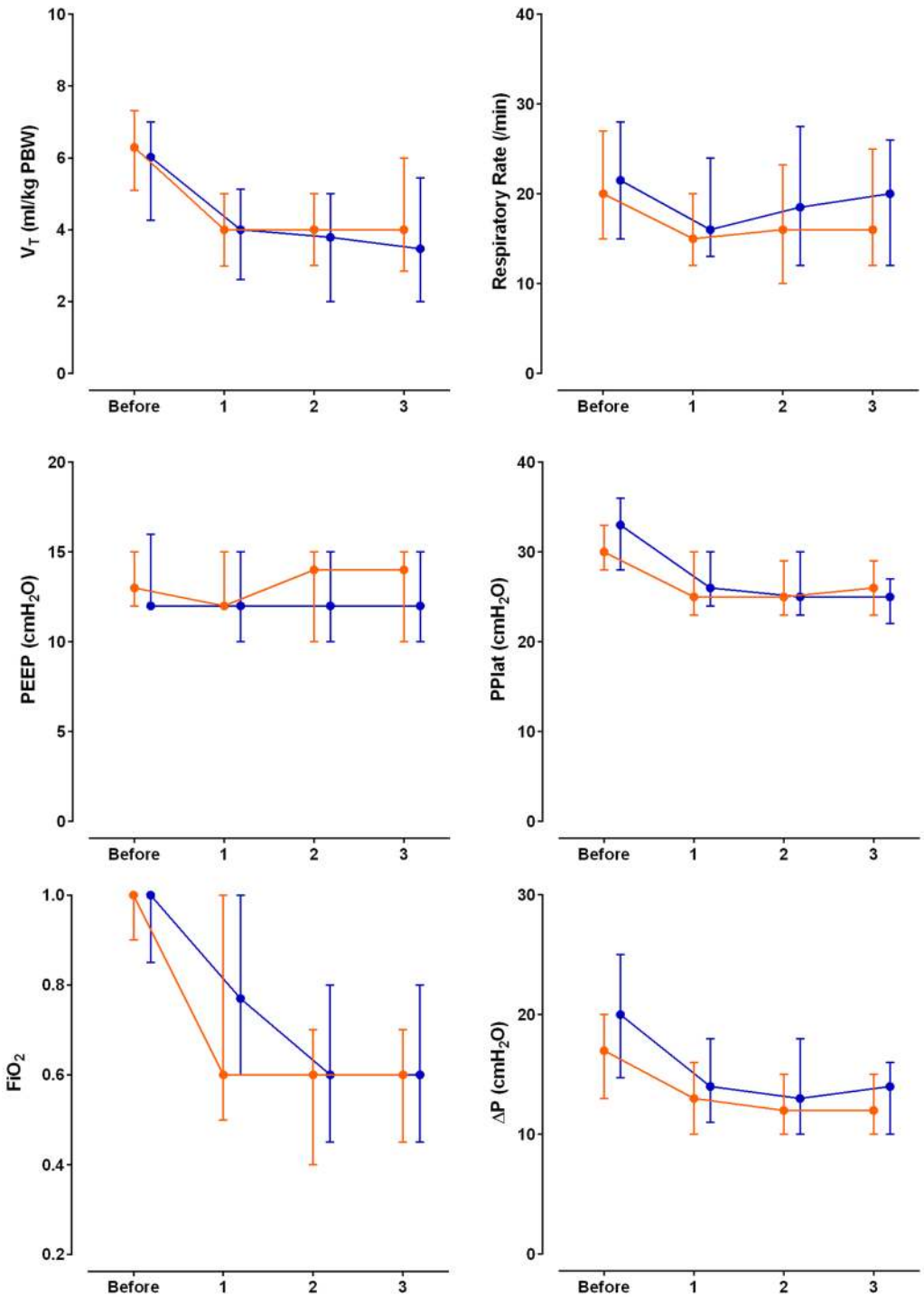

Fig. 2 Tidal volume size (V_T), respiratory rate, inspired oxygen fractions (FiO_2), positive end-expiratory pressure (PEEP) levels, plateau pressure (Pplat) levels, and driving pressure (ΔP) in survivors (*orange line*) and non-survivors (*blue line*) during extracorporeal membrane oxygenation for the acute respiratory distress syndrome. *Before* before extracorporeal membrane oxygenation; days *1*, *2* and *3*, the first, second and third day of ECMO; data are presented as medians and their interquartile ranges, and only for patients that were still receiving ECMO

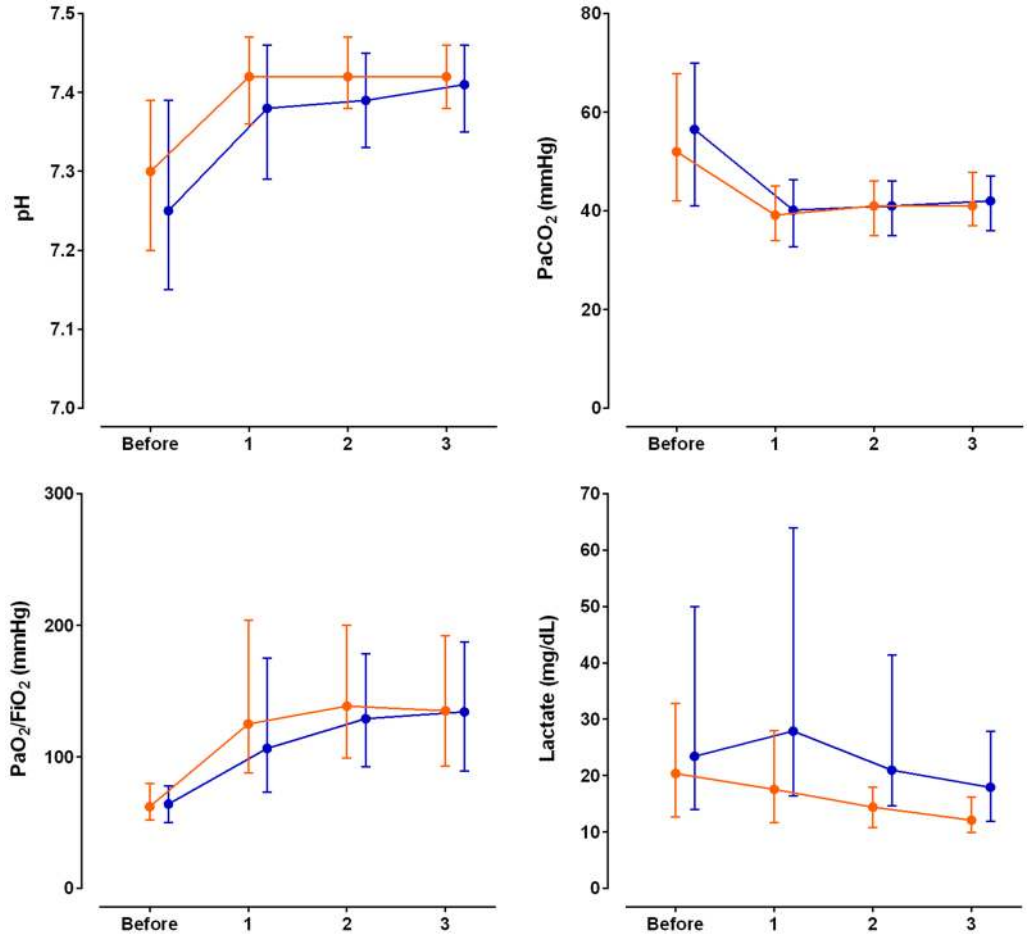

Fig. 3 PaO_2/FiO_2, $PaCO_2$ levels, pHa, and lactate levels in survivors (*orange line*) and non-survivors (*blue line*) during extracorporeal membrane oxygenation (ECMO) for the acute respiratory distress syndrome. *Before* before extracorporeal membrane oxygenation; days *1*, *2* and *3*, the first, second and third day of ECMO; data are presented as medians and their interquartile ranges, and only for patients that were still receiving ECMO

study populations, with diverse indications of ECMO and dissimilar approaches to ECMO and ventilatory management, may further limit the inferences that can be drawn from the present analysis. While grouping patients from several centers around the world may improve the study's generalizability, the fact that most studies were conducted in expert centers may also serve to limit generalizability outside of these settings. Prone position has clearly been shown to benefit patients with severe ARDS [44], and proning could have affected the results of this analysis. Information on proning was unfortunately largely lacking in the databases. However, proning of patients receiving extracorporeal blood treatment was, at least until recently, model hardly performed. Finally, the impact of ventilatory parameters in the subgroup of patients with intracranial hemorrhage or severe bleeding events was not specifically addressed in the present study.

In conclusion, the results from this analysis suggest that a low ΔP during ECMO is independently associated with improved in-hospital survival in patients with ARDS treated with ECMO. Randomized controlled trials should test if strategies aiming at low ΔP during ECMO are safe, feasible and effective in improving outcome of ARDS patients with refractory hypoxemia.

Table 3 Multivariable time-dependent frailty model with in-hospital mortality as the primary outcome

	HR (95 %CI), *p*
Age, years	1.01 (1.00–1.02), 0.006
Gender, male	1.63 (1.21–2.21), 0.001
BMI, kg/m^2	0.95 (0.93–0.97), <0.001
Risk of death, %[a]	1.01 (0.99–1.01), 0.063
SOFA	1.03 (0.98–1.07), 0.252
Time between MV-ECMO	
≤24 h	1.00 (Reference)
24–72 h	0.70 (0.45–1.09), 0.112
>72 h	0.78 (0.58–1.05), 0.103
Indication of ECMO	
Hypoxemia	0.96 (0.34–2.70), 0.935
Hypercapnia	1 (Reference)
Ventilatory parameters	
PEEP, cmH_2O	–
FiO_2, %	0.96 (0.40–2.30), 0.924
Driving pressure, cmH_2O	1.06 (1.03–1.10), <0.001
Respiratory rate, bpm	–
Laboratory parameters	
PaO_2/FiO_2, mmHg	1.00 (0.99–1.00), 0.431
$PaCO_2$, mmHg	0.99 (0.99–1.01), 0.891
Lactate, mg/dL	1.00 (1.00–1.01), 0.005
Hemodynamics (pre-ECMO)	
Norepinephrine, µg/kg/min[b]	1.07 (0.88–1.29), 0.518

The cluster effects induced by the structure of the data were taken into account through random effects in all models

ECMO extracorporeal membrane oxygenation, *BMI* body mass index, *SOFA* sequential organ failure assessment, *MV* mechanical ventilation, *PEEP* positive end-expiratory pressure, *BPM* breaths per minute, *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, FiO_2 inspired fraction of oxygen, *HR* hazard ration

[a] Predicted by APACHE II, APACHE III, SAPS II or SAPS III

[b] Defined as total dose during whole day divided by weight and 1440 min

Electronic supplementary material

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Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

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