Lung-protective ventilation in intensive care unit and operation room

Tidal volume size, level of positive end-expiratory pressure and driving pressure

Serpa Neto, A.

Publication date
2017
Document Version
Other version
License
Other

Chapter 15

Impact of ventilator settings in patients with ARDS undergoing extracorporeal carbon dioxide removal: A pooled individual patient data analysis

Serpa Neto A, Bein T, Lubnow M, Quintel M, Ranieri VM, Ried M, Slutsky AS, Terragni PP, Weber-Carstens S, Gama de Abreu M, Pelosi P, Schultz MJ; for the PROVE Network Investigators

Submitted for publication

Abstract

Purpose: Low-flow extracorporeal carbon dioxide removal ($ECCO_2R$) could facilitate tidal volume reduction, improving lung protection and thus outcome in patients with acute respiratory distress syndrome (ARDS). The aim of this investigation was to describe changes in mechanical ventilator settings after start of $ECCO_2R$ and their associations with outcome in patients with ARDS.

Methods: We performed an individual patient data metaanalysis of studies in patients with ARDS receiving $ECCO_2R$. Changes in ventilator settings were assessed. The primary end-point was ventilator-free days and alive at day 60 (VFD-60). A multi-level multivariable linear model was used to determine which ventilation variables were independently associated with VFD-60.

Results: Five studies including 129 patients were included in the final analysis. Start of $ECCO_2R$ was accompanied by decreases in tidal volume, plateau pressure, driving pressure, respiratory rate as well as minute ventilation, and resulted in higher pHa and lower $PaCO_2$. Advanced age and time interval between start of ventilation and of $ECCO_2R$ were independently associated with less VFD-60. A lower driving pressure during $ECCO_2R$ was associated with higher VFD-60.

Conclusions: In ARDS patients treated with $ECCO_2R$, both shorter time interval between start of ventilation and of $ECCO_2R$, as well as lower driving pressure during $ECCO_2R$ were associated with higher VFD-60.

Introduction

So-called 'lung-protective' mechanical ventilation aiming at prevention of alveolar overdistension by using low tidal volumes of 6 ml/kg predicted body weight (PBW) has been found to improve outcome in patients with acute respiratory distress syndrome (ARDS).[1,2] However, even during ventilation with low tidal volumes overdistension can still occur,[3-6] suggesting that further reductions in tidal volume could result in more benefit in certain patients.[7.8] Unfortunately, tidal volume reduction to < 6 ml/kg PBW could be difficult if not impossible in patients with hypercapnia,[5,6,8] or metabolic acidosis.[5]

Low-flow extracorporeal carbon dioxide removal ($ECCO_2R$) using an artificial membrane for gas exchange, mainly of CO_2, is a relative simple and safe intervention that could facilitate tidal volume reductions < 6 ml/kg PBW,[6,8] as such having the potential to further improve outcome in ARDS patients.[8,9] In a randomized controlled trial (RCT) of $ECCO_2R$ using ultra-protective low tidal volumes of 3 ml/kg PBW the number of ventilator-free days and alive at day 60 (VFD-60) increased in patients with severe ARDS.[9] It is uncertain, however, whether factors other than tidal volume size during low-flow $ECCO_2R$ are associated with outcome in ARDS patients.

Recently, driving pressure was described as an important parameter associated with outcome in patients with ARDS[10] and also in those receiving extracorporeal membrane oxygenation (ECMO) for refractory hypoxemia.[11,12] As yet, no study assessed the impact of this ventilatory variable and outcome of patients receiving $ECCO_2R$.

The aim of this investigation was to describe changes in ventilatory settings following the start of $ECCO_2R$, and to determine which factors are independently associated with VFD-60.

Methods

Setting and patients

We identified eligible studies up to August 2016 through an electronic search by two independent authors using 'MEDLINE', 'Cumulative Index to Nursing and Allied Health

Literature' (CINAHL), and 'Cochrane Central Register of Controlled Trials' (CENTRAL). All investigations describing ventilation practice in adult ARDS patients undergoing $ECCO_2R$ were considered for inclusion. The 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 and Jadad score for the RCT.

Data collection

The following variables were assessed for each patient: 1) demographic and baseline data, including severity of hypercapnia and metabolic acidosis; 2) time interval between start of ventilation and of $ECCO_2R$, 3) daily $ECCO_2R$ settings until weaning of support (e.g., blood flow and sweep gas flow); 4) ventilator settings before and daily after start of $ECCO_2R$; 5) complications of $ECCO_2R$, and 6) clinical outcomes (ICU and hospital length of stay, bleeding events and in-hospital mortality). Data were collected before and daily after start of $ECCO_2R$, at a fixed moment in the morning as per protocol of the original studies.

Definitions

Driving pressure (ΔP) was calculated as inspiratory plateau pressure (Pplat) minus the PEEP level (as measured in the ventilator) in absence of spontaneous breathing, as evaluated clinically.

Outcome parameters

The primary outcome variable was VFD-60, calculated as the number of days from weaning off invasive ventilation and alive to day 60. Patients who died before weaning were deemed to have zero VFD-60. Secondary outcome variables included: 1) $ECCO_2R$-free days at day 28 (EFD-28), calculated as the number of days from weaning off $ECCO_2R$ to day 28, where patients who died before weaning of $ECCO_2R$ were deemed to have no EFD-28; 2) ICU length of stay; 3) hospital length of stay; 4) bleeding events; 5) intracranial haemorrhage; and 6) in-hospital mortality.

Analysis plan

Ventilator settings before and after start of $ECCO_2R$ were described and compared. Time interval between start of mechanical ventilation and of $ECCO_2R$ was categorized according

to tertiles. Next, associations between ventilatory and non ventilatory variables at the first day of $ECCO_2R$ and VFD-60 were analyzed.

Statistical analysis

Normally distributed data were described as mean ± standard deviation while no-normally distributed data were described as median (quartile range [QR = 25% - 75%]). Categorical variables were described as proportions (%). Continuous variables were compared using independent or paired Student t tests, analysis of variance, Mann-Whitney test or Kruskal-Wallis test according to the distribution of the variables. Categorical variables were compared using chi-square or Fisher exact tests. Ventilator settings before and after start of ECCO2R were plotted in distribution graphs.

Multiple imputation was conducted to deal with missing values in the retrieved database, including age, gender, BMI, risk of death, Sequential Organ Failure Assessment score (SOFA), chronic obstructive pulmonary disease (COPD), diabetes mellitus, time between start of mechanical ventilation and $ECCO_2R$, 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, $PaCO_2$, pHa, PaO_2/FiO_2, lactate, duration of mechanical ventilation and $ECCO_2R$, 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 five databases after multiple imputation.

A multivariable model was built to quantify the association between predefined ventilatory variables and VFD-60, while controlling for other known risk factors. We conducted multi-level analyses to adjust for clustering of the data. Therefore, a linear model was used to determine predictors of VFD-60 by modelling it as the dependent variable. Independent variables were selected when the univariate analysis p value was < 0.2. Then, a multivariable linear model (presented as β coefficient and 95% confidence interval [CI]) considering the variables at day 1 after $ECCO_2R$ beginning was built with study treated as random effect. 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 a $p < 0.05$.

Since static compliance, Pplat level and ΔP showed high collinearity we chose to include only ΔP in the model. This choice is due to recent studies and one individual patient data meta-analysis suggesting that ΔP is the ventilatory variable that best stratifies risk of death in ARDS patients receiving mechanical ventilation.[10-12] Also, PaO_2/FiO_2 and FiO_2 showed high collinearity and we chose to include only PaO_2/FiO_2 in the model, as it could provide more information on severity of lung injury than the FiO_2 alone. We conducted a post–hoc analysis replacing ΔP by Pplat level to assess the additional impact of the later ventilatory variable. We compared the two models and assessed the fit of each model.

We performed one post–hoc analysis, in which we determined which factors before start of $ECCO_2R$ showed an association with a change in ΔP associated with start of $ECCO_2R$. A multivariable model was built to quantify the association between baseline characteristics and ventilatory variables and the change in ΔP after start of $ECCO_2R$, while controlling for other known risk factors. We conducted multi-level analyses to adjust for clustering of the data. Therefore, a linear regression model was used to determine predictors of change in ΔP after $ECOO_2R$ start by modelling 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 linear regression model (presented as β coefficient and 95% confidence interval [CI]) considering the variables before $ECCO_2R$ beginning was built with study treated as random effect. 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 a $p < 0.05$.

We used SPSS v.20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) and R v.2.12.0 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses, and used a two–sided $p < 0.05$ to determine whether differences were statistical significant.

Results

Selection and characteristics of studies

The search identified 59 observational studies. Fifty studies were not included due to the following reasons: case report (n = 17); review (n = 17); use of extracorporeal membrane oxygenation (ECMO) (n = 9); others (n = 7) (eFigure 1). Four other studies were excluded because it was not possible to obtain individual patient data. Data from the remaining five investigations were retrieved from databases sent by the corresponding authors. A total of 129 patients were pooled.[8,9,13-15] The characteristics of the included studies are shown in eTable 1 and 2. In only one study a blood pump was used to achieve a low blood flow,[10] the other studies used pumpless devices.

Characteristics of the patients

Patient characteristics are presented in Table 1. Median time interval from start of mechanical ventilation until initiation of $ECCO_2R$ was 72 (24–144) hours (Table 1). As shown in Table 2, the number of VFD-60 ranged from 0 to 48 days with a median value of 34 days. Secondary outcomes are presented in Table 2. The number of EFD-28 was 20 (0–23) days, and hospital length of stay was 31 (21–47) days. In-hospital mortality was 30.2%. The number of reported bleeding events, including intracranial hemorrhage, was very low (2.3%) (Table 2).

Ventilator settings before and after initiation of $ECCO_2R$

eTable 3 shows ventilator settings before and after $ECCO_2R$ initiation. Initiation of $ECCO_2R$ was accompanied by significant decreases in tidal volume, Pplat and ΔP, respiratory rate, minute-ventilation and FiO_2 (eTable 3, Figure 1). Initiation of $ECCO_2R$ resulted in a significant decrease in $PaCO_2$ levels, and increases in pHa and mean arterial pressure (eTable 3, Figure 2). PEEP levels were not altered, and PaO_2/FiO_2 ratio and static compliance did not change (eTable 3, Figure 1 and 2).

Association between ventilatory, non-ventilatory factors and VFD-60

Results of the univariable analysis of ventilatory and non-ventilatory factors during $ECCO_2R$ associated with VFD-60 are provided in eTable 4. After adjusting for confounders,

independent predictors of less VFD-60 included higher age, longer duration between ventilation and initiation of $ECCO_2R$ and higher ΔP (Table 3).

Post-hoc analysis

Replacing ΔP by Pplat levels, higher age, longer duration between ventilation and initiation of $ECCO_2R$ and higher Pplat levels were independently associated with less VFD-60 (eTable 5). When we include Pplat and ΔP in the same model, none of the variables were significant (eTable 6). However, there was a trend with ΔP in comparison to Pplat (p = 0.070 vs. p = 0.344) (eTable 7). The comparison of the models is shown in eTable 6.

Results of the univariable analysis of ventilatory and non-ventilatory factors before $ECCO_2R$ associated with a change in ΔP after $ECCO_2R$ beginning are provided in eTable 8. After adjusting for confounders, only ΔP itself before start of $ECCO_2R$ showed an independent association with a change in ΔP after $ECCO_2R$ beginning (eTable 8).

Discussion

The main finding of this analysis in a large cohort of ARDS patients undergoing $ECCO_2R$ is that age, time interval between start of ventilation and $ECCO_2R$, and ΔP at the first day were independently associated with VFD-60.

With $ECCO_2R$ it is possible to increase protection of the lungs by using very low tidal volumes, resulting in lower airway pressure and lower ΔP levels, thereby further decreasing the iatrogenic consequences of mechanical ventilation.[1-7] A lower ΔP during $ECCO_2R$ was associated with improved outcomes, consistent with studies in patients with ARDS not treated with extracorporeal techniques ,[10,16,17] and in patients with ARDS receiving ECMO for refractory hypoxemia,[11,12] but also patients undergoing general anesthesia for surgery.[18] The results of all these analyses build upon 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 ΔP levels and lung injury .[19,20] The decline in ΔP levels after initiation of $ECCO_2R$ was established largely by tidal volume reductions, but the present analysis found only an association between ΔP levels

and outcome, which was independent of other factors. In the present study we also found an important association between age and worse outcome. In fact, age is an important factor that affects the outcome in almost all diseases, and it is unlikely that $ECCO_2R$ is an exception, as $ECCO_2R$ implementation imposes great physiologic stress on the patients. This association was also described in other studies in patients undergoing ECMO and is considered in a prognostic score.[21-24]

Consistent with findings from previous investigations of ECMO in ARDS patients,[24-31] the present study suggests an association between duration of ventilation prior to initiation of $ECCO_2R$ and outcome. Indeed several studies suggest a direct relationship between duration of mechanical ventilation prior to ECMO initiation and mortality, and consequently the PRedicting dEath for SEvere ARDS on VV-ECMO (PRESERVE) score as well as the Respiratory ECMO Survival Prediction (RESP) use the number of days of mechanical ventilation to predict outcomes in ARDS patients who may need extracorporeal treatment.[24,29] Ongoing randomized controlled trials of ECMO in ARDS patients may help to confirm the suggestion that early use of ECMO may be more beneficial,[32] and this confirmation is also highly needed for $ECCO_2R$.

Since it is not possible to adopt ventilation to the protective 'demands' of different lung regions, with heterogeneous spread of lung injury, an approach using 6 mL/kg PBW of tidal volume may not be protective enough.[3-7,33] Indeed, a recent study showed that use of tidal volumes below 6 ml/kg PBW with use of $ECCO_2R$ reduces lung weight, reduces the amounts of overdistended, non–aerated, and poorly aerated lung parts, and increases the amount of normally aerated lung parts.[8]

The result of the present analysis echo findings from a recent RCT showing that an ultra-protective ventilation strategy during $ECCO_2R$ in ARDS patients is feasible and safe, and even seemed to result in better outcomes.[9] Indeed, in this RCT the use of tidal volumes of 3 mL/kg PBW during $ECCO_2R$ was associated with more VFD-60 as compared to ventilation using tidal volumes of 6 mL/kg PBW in patients with more severe hypoxemia

patients, though it should be mentioned that this part of the analysis was decided post–hoc.[9] Unfortunately, the ΔP was not assessed in that study.

Recently, it was described in an animal model of severe ARDS that the use of so-called 'ultra-protective ventilation' with tidal volumes of 3 mL/kg PBW combined with $ECCO_2R$ and in the absence of spontaneous breathing reduced lung histology damage.[34] These findings suggest that ultra-protective ventilation during $ECCO_2R$ was more protective and this could be related to a lower driving pressure with this strategy of ventilation.[34]

In recent years, techniques of extracorporeal lung support have become easier and safer to use, with smaller cannulas and greater efficacy. Compared to ECMO, $ECCO_2R$ is much simpler and easier to use due to its small size, lack of pumps and the possibility to integrate with other supportive techniques like hemofiltration.[35] The relatively low rate of complications in the present analysis is in accordance with those in other reports on $ECCO_2R$.[9,36]

The present analysis has several limitations, including its non-randomized design, which precludes any inference of causality regarding the association between ventilatory variables 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 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 within each 24-hour slot, especially shortly after start of $ECCO_2R$. Also, the fact that ΔP could represent not more than a marker of disease severity should be taken in account. Heterogeneity of the different study populations, the diverse indications of $ECCO_2R$ and dissimilar approaches to $ECCO_2R$ 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 study's generalizability, the fact that most studies were conducted in expert centers may also serve to limit generalizability outside of these settings.

In conclusion, the results from this individual patient data meta-analysis suggest that, in patients with ARDS treated with $ECCO_2R$, a shorter time interval between start of

ventilation and $ECCO_2R$ and low ΔP during $ECCO_2R$ are independently associated with VFD-60. Randomized controlled trials should test if strategies aiming at earlier start of $ECCO_2R$, and lower ΔP levels during $ECCO_2R$ are safe, feasible and effective in improving outcome of ARDS patients.

Table 1 – Baseline characteristics of the patients

Age, years	46.8 ± 14.0
Gender, male	118 / 129 (91.5)
BMI, kg/m^2	28.0 ± 4.5
Actual weight, kg	86.5 ± 15.5
PBW, kg	71.0 ± 8.7
Risk of death, %*	32.2 ± 22.5
SOFA	9.6 ± 3.8
LIS	3.2 ± 0.6
Co-Morbidities	
COPD	7 / 103 (6.8)
Diabetes	5 / 103 (4.9)
Hypertension	20 / 103 (19.4)
CAD	4 / 103 (3.9)
HIV	0 / 63 (0.0)
H_1N_1	0 / 89 (0.0)
Time between MV-ECCO_2R, hours	72.0 (24.0 – 144.0)
≤ 24 hours	33 / 126 (26.2)
24 – 72 hours	38 / 126 (30.2)
> 72 hours	55 / 126 (43.7)
Severity of ARDS	
Mild	5 / 129 (3.9)
Moderate	66 / 129 (51.2)
Severe	58 / 129 (45.0)
Type of ARDS	
Pulmonary	73 / 129 (56.6)
No-Pulmonary	56 / 129 (43.4)
Cause of ARDS	
Pneumonia	59 / 129 (45.7)
Non-Pulmonary Sepsis	13 / 129 (10.1)
Trauma	39 / 129 (30.2)
Other	18 / 129 (14.0)

ECCO_2R: extracorporeal carbon dioxide removal; 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;

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

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

Table 2 – Clinical outcomes of patients under $ECCO_2R$

Primary outcome	
Ventilator-free days at day 60	34.0 (0.0 – 48.2)
Secondary outcomes	
$ECCO_2R$-free days at day 28	20.0 (0.0 – 23.0)
ICU length of stay	22.0 (15.2 – 34.0)
Hospital length of stay	31.0 (21.0 – 47.0)
Bleeding events	3 / 129 (2.3)
Intracranial hemorrhage	0 / 129 (0.0)
In-hospital mortality	39 / 129 (30.2)

$ECCO_2R$: extracorporeal carbon dioxide removal; ICU: intensive care unit

Data shown as median (interquartile range) or number (percentage)

Table 3 – Multivariable linear regression with ventilator-free days at day 60 as the primary outcome[a]

	β Coefficient (95% CI), *p*
Age, years	-0.46 (-0.72 to -0.20), < 0.001
Gender, male	1.29 (-10.20 to 12.78), 0.739
BMI, kg/m^2	0.39 (-0.40 to 1.18), 0.327
Risk of death, %*	-0.17 (-0.42 to 0.08), 0.189
SOFA	-1.30 (-3.16 to 0.55), 0.163
Time between MV-$ECCO_2R$	
≤ 24 hours	1 (Reference)
24 – 72 hours	-2.48 (-11.57 to 6.61), 0.592
> 72 hours	-11.28 (-19.70 to -2.87), 0.009
Ventilatory Parameters at the first day	
Tidal volume, ml/kg PBW	-0.76 (-3.45 to 1.94), 0.577
Driving pressure, cmH_2O	-1.58 (-2.83 to -0.33), 0.014
Minute-ventilation, l/min	0.81 (-1.00 to 2.63), 0.371
Laboratory Parameters at the first day	
$PaCO_2$, mmHg	-0.04 (-0.31 to 0.23), 0.774
Lactate, mg/dL	-0.06 (-0.22 to 0.10), 0.416

$ECCO_2R$: extracorporeal carbon dioxide removal; BMI: body mass index; SOFA: sequential organ failure assessment; MV: mechanical ventilation; BPM: breaths per minute; CI: confidence interval; FiO_2: inspired fraction of oxygen; PBW: predicted body weight

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

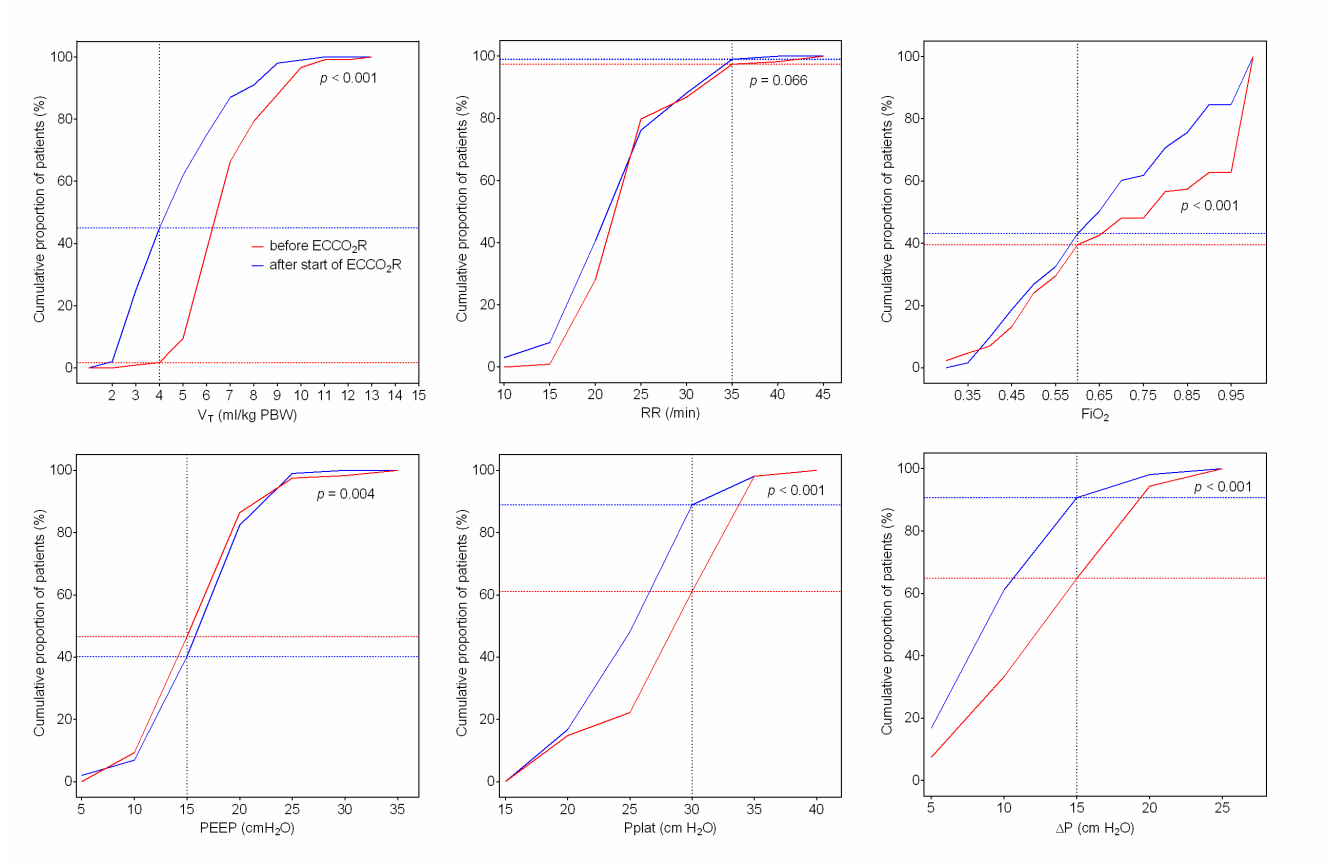
[a] analysis after multiple imputation

Figure Legends

Figure 1 – Ventilatory variables before and after $ECCO_2R$ initiation

Figure 2 – Laboratorial variables before and after $ECCO_2R$ initiation

Figure 1 – Ventilatory variables before and after $ECCO_2R$ initiation



Cumulative frequency distribution of tidal volume, respiratory rate, FiO_2, PEEP, plateau pressure and driving pressure. After the start of $ECCO_2R$, there was an increase in the percentage of patients ventilated with tidal volume below 4 ml/kg PBW (45.0% vs 1.7%; $p < 0.001$), FiO_2 below 0.60 (43.1% vs. 39.5%; $p < 0.001$), Pplat below 30 cmH_2O (88.9% vs. 61.1%; $p < 0.001$) and ΔP below 15 cmH_2O (90.7% vs. 64.8%; $p < 0.001$).

Abbreviations: PEEP: positive end–expiratory pressure; PBW: predicted body weight; V_T: tidal volume; RR: respiratory rate; FiO_2: inspired fraction of oxygen; Pplat: plateau pressure; ΔP: driving pressure

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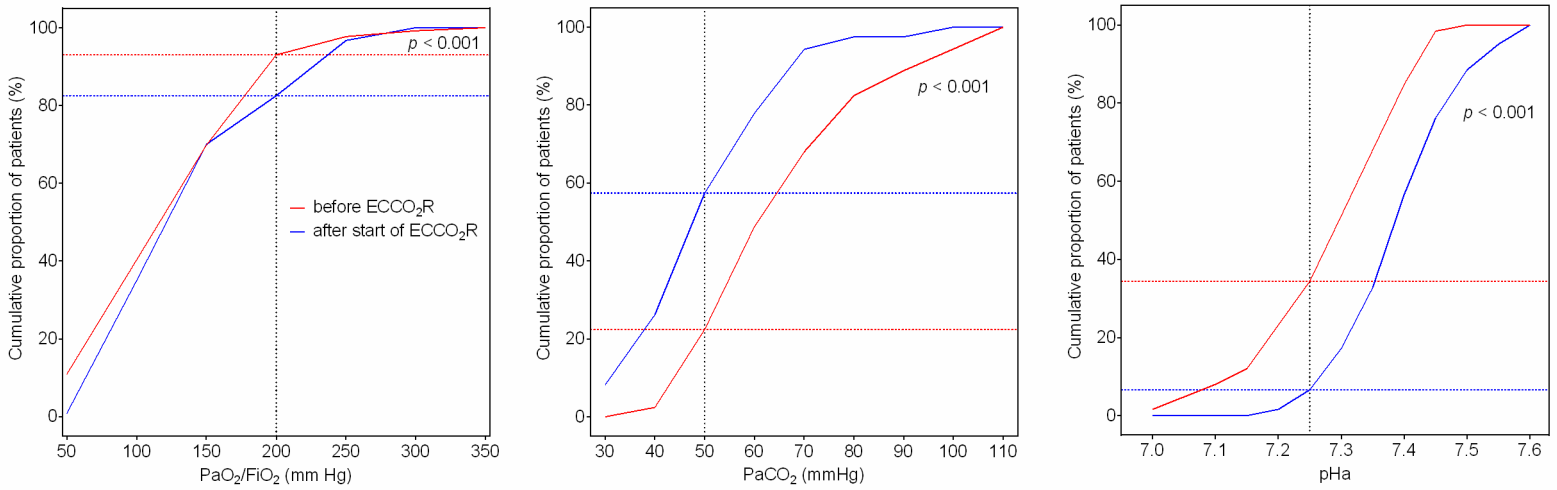
Figure 2 – Laboratorial variables before and after $ECCO_2R$ initiation



Cumulative frequency distribution of PaO_2 / FiO_2, $PaCO_2$ and pHa. After the start of $ECCO_2R$, there was an increase in the percentage of patients with $PaCO_2$ below 50 mmHg (57.4% vs. 22.4%; $p < 0.001$), a PaO_2 / FiO_2 above 200 mmHg (17.5% vs. 7.0%; $p < 0.001$) and a pHa above 7.25 (93.4% vs. 65.6%; $p < 0.001$).

References

1. Acute Respiratory Distress Syndrome Network. 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; 342:1301–18.

2. Putensen C, Theuerkauf N, Zinserling J, Wrigge H, Pelosi P. Meta-analysis: ventilation strategies and outcomes of the acute respiratory distress syndrome and acute lung injury. *Ann Intern Med* 2009; 151:566-76.

3. Grasso S, Stripoli T, De Michele M, et al. ARDSNet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med* 2007; 176:761–7.

4. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2007; 175:160-6.

5. Retamal J, Libuy J, Jiménez M, et al. Preliminary study of ventilation with 4 ml/kg tidal volume in acute respiratory distress syndrome: feasibility and effects on cyclic recruitment - derecruitment and hyperinflation. *Crit Care* 2013; 17:R16.

6. Fanelli V, Ranieri MV, Mancebo J, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care* 2016; 20:36.

7. Hager DN, Krishnan JA, Hayden DL, Brower RG; ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005; 172:1241–5.

8. Terragni PP, Del Sorbo L, Mascia L, et al. Tidal volume lower than 6 ml/kg enhances lung protection: role of extracorporeal carbon dioxide removal. *Anesthesiology* 2009; 111:826-35.

9. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (˜3 ml/kg) combined with extracorporeal CO2 removal versus 'conventional' protective ventilation (6

ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med* 2013; 39:847-56.

10. Amato MB, Meade MO, Slutsky AS, et al. Driving Pressure as a mediator of survival in patients with Acute Respiratory Distress Syndrome (ARDS). *N Engl J Med* 2015; 372:747-55.

11. Serpa Neto A, Schmidt M, Azevedo LC, et al. 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. *Intensive Care Med* 2016; 42:1672-1684.

12. Schmidt M, Stewart C, Bailey M, et al. Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: a retrospective international multicenter study. *Crit Care Med* 2015; 43:654-64.

13. Bein T, Zimmermann M, Philipp A, et al. Addition of acetylsalicylic acid to heparin for anticoagulation management during pumpless extracorporeal lung assist. *ASAIO J* 2011; 57:164-8

14. Ried M, Bein T, Philipp A, et al. Extracorporeal lung support in trauma patients with severe chest injury and acute lung failure: a 10-year institutional experience. *Crit Care* 2013; 17:R110.

15. Lubnow M, Luchner A, Philipp A, et al. Combination of high frequency oscillatory ventilation and interventional lung assist in severe acute respiratory distress syndrome. *J Crit Care* 2010; 25:436-44.

16. Estenssoro E, Dubin A, Laffaire E, et al. Incidence, clinical course, and outcomes in 217 patients with acute respiratory distress syndrome. *Crit Care Med* 2002; 30:2450-6

17. Boissier F, Katsahian S, Razazi K, et al. Prevalence and prognosis of cor pulmonale during protective ventilation for acute respiratory distress syndrome. *Intensive Care Med* 2013; 39:1725-33.

18. Neto AS, Hemmes SN, Barbas CS, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical

ventilation for general anaesthesia: a meta-analysis of individual patient data. *Lancet Respir Med* 2016; 4:272-80.

19. Tschumperlin DJ, Oswari J, Margulies AS. Deformation-induced injury of alveolar epithelial cells. Effect of frequency, duration, and amplitude. *Am J Respir Crit Care Med* 2000; 162:357-62.

20. Samary CS, Santos RS, Santos CL, et al. Biological Impact of Transpulmonary Driving Pressure in Experimental Acute Respiratory Distress Syndrome. *Anesthesiology* 2015; 123:423-33.

21. Lan C, Tsai PR, Chen YS, Ko WJ. Prognostic factors for adult patients receiving extracorporeal membrane oxygenation as mechanical circulatory support--a 14-year experience at a medical center. *Artif Organs* 2010; 34:E59-64.

22. Chen YC, Tsai FC, Chang CH, et al. Prognosis of patients on extracorporeal membrane oxygenation: the impact of acute kidney injury on mortality. *Ann Thorac Surg* 2011; 91:137-42.

23. Liu X, Xu Y, Zhang R, Huang Y, et al. Survival Predictors for Severe ARDS Patients Treated with Extracorporeal Membrane Oxygenation: A Retrospective Study in China. *PLoS One* 2016; 11:e0158061.

24. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 2014; 189:1374-82.

25. Beiderlinden M, Eikermann M, Boes T, Breitfeld C, Peters J. Treatment of severe acute respiratory distress syndrome: Role of extracorporeal gas exchange. *Intensive Care Med* 2006; 32:1627–31.

26. Pappalardo F, Pieri M, Greco T, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. *Intensive Care Med* 2013; 39:275-81.

27. Hemmila MR, Rowe SA, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg* 2004; 240:595-605.

28. Pranikoff T, Hirschl RB, Steimle CN, Anderson HL 3rd, Bartlett RH. Mortality is directly related to the duration of mechanical ventilation before the initiation of extracorporeal life support for severe respiratory failure. *Crit Care Med* 1997; 25:28-32.

29. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med* 2013; 39:1704-13.

30. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. *Intensive Care Med* 2009; 35:2105-14.

31. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 2014; 189:1374-82

32. Combes A. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA). Available at: http://www.clinicaltrials.gov/ct2/show/nct01470703?term=eolia1ecmo&rank=1. Accessed February 24, 2017.

33. Grasso S, Stripoli T, Sacchi M, et al. Inhomogeneity of lung parenchyma during the open lung strategy: a computed tomography scan study. *Am J Respir Crit Care Med* 2009; 180:415–23.

34. Güldner A, Kiss T, Bluth T, et al. Effects of ultraprotective ventilation, extracorporeal carbon dioxide removal, and spontaneous breathing on lung morphofunction and inflammation in experimental severe acute respiratory distress syndrome. *Anesthesiology* 2015; 122:631-46.

35. Godet T, Combes A, Zogheib E, et al. Novel carbon dioxide removal device driven by a renal-replacement system without hemofilter: an experimental approach and validation. *Crit Care* 2014; 18:P316.

36. Zimmermann M, Bein T, Arlt M, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care* 2009; 13:R10

Supplementary Appendix to 'Impact of ventilator settings in patients with ARDS undergoing extracorporeal carbon dioxide removal: A pooled individual patient data analysis'

CALCULATION OF PREDICTED MORTALITY FROM SAPS II AND APACHE II

- *SAPS II:*

logit = -7.7631 + 0.0737 * Score + 0.9971 * ln(Score + 1)

Mortality = e^{logit} / 1 + e^{logit}

- *APACHE II:*

x = -3.517 + (0.146 * Score) + 0.603 (if emergency surgery) + (Admission Indication Weight)

ln(R / 1 – R) = x → R / 1 – R = e^{x} (solve for R…)

R (percent mortality) = e^{x} / 1 + e^{x} *100

eTable 1 – Characteristics of the included studies

Author	Year	Design	Type of Device	$ECCO_2R$*		ELSO Member**	NOS / Jadad
				N	Mortality, %		
Terragni	2009	Observational	Low-flow	11	63.6	No	04
Lubnow	2010	Observational	Pumpless	21	52.4	Yes	05
Bein	2011	Observational	Pumpless	31	25.8	Yes	06
Ried	2013	Observational	Pumpless	26	23.1	Yes	06
Bein	2013	RCT	Pumpless	40	17.5	Yes	02

RCT: randomized controlled trial; $ECCO_2R$: extracorporeal carbon dioxide removal; NOS: Newcasttle Ottawa Scale

*: data based on the database provided by the authors and not described in the studies (discrepancies may occur)

**: checked September 20, 2016 (https://www.elso.org)

eTable 2 – Detailed characteristics of the included studies

Author, Year	Age, years	Risk of Death, %	Pneumonia, %	Duration of Ventilation*, hours	Duration of Ventilation, days	Duration of $ECCO_2R$, days	Hospital LOS, days	ICU LOS, days	Weaned from $ECCO_2R$, %
Terragni, 2009	56.5	43.6	45.5	97.1	27.2	5.6	38.7	30.7	90.9
Lubnow, 2010	50.1	33.9	85.7	144.9	25.6	6.7	34.7	27.6	90.5
Bein, 2011	47.6	27.7	41.9	126.8	17.4	8.1	33.8	28.8	100.0
Ried, 2013	34.5	30.0	0.0	101.2	18.7	7.6	33.3	26.6	92.3
Bein, 2013	49.7	32.9	57.5	89.4	27.2	7.6	47.0	30.3	97.5

* before $ECCO_2R$

eTable 3 – Ventilatory parameters *before* and *after* $ECCO_2R$

	Before $ECCO_2R$	After $ECCO_2R$	*p* value[a]
Mode of Ventilation			
Pressure-Controlled	22 / 129 (18.1)	7 / 129 (5.6)	0.023
Volume-Controlled	89 / 129 (68.1)	88 / 129 (68.1)	
Other	18 / 129 (13.9)	34 / 129 (26.4)	
Ventilatory Parameters			
Tidal volume, ml/kg PBW	7.2 ± 1.7	5.1 ± 1.9	< 0.001
PEEP, cmH_2O	16.4 ± 4.7	16.7 ± 4.3	0.405
FiO_2, %	0.7 ± 0.2	0.7 ± 0.2	0.002
Plateau pressure, cmH_2O	28.1 ± 5.0	25.8 ± 4.5	0.001
Driving pressure, cmH_2O	12.9 ± 5.4	9.6 ± 4.9	< 0.001
Respiratory rate, bpm	26.0 ± 12.7	22.8 ± 7.2	0.018
Minute-Ventilation, l/min	12.8 ± 5.7	8.0 ± 3.3	< 0.001
Static compliance*	51.2 ± 27.9	50.6 ± 30.9	0.741
Laboratory Parameters			
PaO_2, mmHg	80.6 ± 23.2	84.1 ± 31.6	0.315
PaO_2 / FiO_2, mmHg	124.0 ± 62.5	133.3 ± 57.6	0.095
$PaCO_2$, mmHg	65.0 ± 17.9	49.5 ± 14.3	< 0.001
pHa	7.28 ± 0.11	7.39 ± 0.09	< 0.001
Lactate, mg/dL	24.2 ± 26.3	27.8 ± 34.6	0.058
Hemodynamics			
MAP, mmHg	73.5 ± 10.0	79.8 ± 12.4	< 0.001
Norepinephrine, µg/kg/min¶	0.58 ± 0.93	0.41 ± 0.80	0.091
$ECCO_2R$ Parameters			
Flow, l/min	---	1.6 ± 0.4	---
Sweep gas flow, l/min	---	9.5 ± 2.9	---

$ECCO_2R$: extracorporeal carbon dioxide removal; PBW: predicted body weight; PEEP: positive end-expiratory pressure; BPM: breaths per minute; MIN: minutes; FiO_2: inspired fraction of oxygen

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

*: static compliance calculated as tidal volume / plateau pressure *minus* PEEP (ml / cmH_2O)

¶: defined as total dose during whole day divided by weight and 1440 minutes

[a]: *p* for before vs. after

eTable 4 – Univariable linear regression with ventilator-free days at day 60 as the primary outcome

	β Coefficient (95% CI), *p* value
Age, years	-0.16 (-0.39 to 0.07), 0.171
Gender, male	8.25 (3.19 to 13.31), 0.002
BMI, kg/m^2	-0.73 (-1.05 to -0.41), < 0.001
Risk of death, %*	-0.12 (-0.17 to -0.08), < 0.001
SOFA	-0.64 (-1.02 to -0.26), 0.001
LIS	-0.39 (-7.18 to 6.40), 0.909
Time between MV-$ECCO_2R$	
≤ 24 hours	1 (Reference)
24 – 72 hours	-1.99 (-5.34 to 1.35), 0.239
> 72 hours	-13.91 (-17.34 to -10.48), < 0.001
Ventilatory Parameters at the first day	
Tidal volume, ml/kg PBW	-1.13 (-1.55 to -0.70), < 0.001
PEEP, cmH_2O	-0.43 (-1.58 to 0.72), 0.455
Plateau pressure, cmH_2O	-1.48 (-1.76 to -1.21), < 0.001
Driving pressure, cmH_2O	-0.91 (-1.63 to -0.19), 0.014
Respiratory rate, bpm	-0.11 (-0.45 to 0.23), 0.518
Minute-Ventilation, l/min	-0.71 (-1.07 to -0.36), < 0.001
Static compliance**	-0.01 (-0.13 to 0.11), 0.842
Laboratory Parameters at the first day	
PaO_2/FiO_2, mmHg	0.00 (-0.01 to 0.01), 0.844
$PaCO_2$, mmHg	-0.12 (-0.29 to 0.05), 0.175
pHa	9.85 (-26.54 to 46.25), 0.592
Lactate, mg/dL	-0.04 (-0.07 to -0.01), 0.014
Hemodynamics (pre-$ECCO_2R$)	
MAP, mmHg	0.03 (-0.11 to 0.18), 0.625
Norepinephrine, µg/kg/min¶	-1.25 (-3.74 to 1.24), 0.320

BMI: body mass index; PBW: predicted body weight; SOFA: sequential organ failure assessment; LIS: lung injury score; MV: mechanical ventilation; PEEP: positive end-expiratory pressure; BPM: breaths per minute; MIN: minutes; HR: hazard ratio; CI: confidence interval, FiO_2: inspired fraction of oxygen

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

**: static compliance calculated as tidal volume / plateau pressure *minus* PEEP (ml / cmH_2O)

¶: defined as total dose during whole day divided by weight and 1440 minutes

eTable 5 – Multivariable linear regression with ventilator-free days at day 60 as the primary outcome replacing driving pressure by plateau pressure[a]

	β Coefficient (95% CI), *p*
Age, years	-0.50 (-0.76 to -0.24), < 0.001
Gender, male	-5.74 (-17.02 to 5.54), 0.318
BMI, kg/m^2	0.60 (-0.18 to 1.39), 0.133
Risk of death, %*	-0.26 (-0.54 to 0.01), 0.063
SOFA	-0.66 (-2.88 to 1.57), 0.550
Time between MV-$ECCO_2R$	
≤ 24 hours	1 (Reference)
24 – 72 hours	-0.46 (-9.48 to 8.56), 0.920
> 72 hours	-8.53 (-16.86 to -0.20), 0.045
Ventilatory Parameters at the first day	
Tidal volume, ml/kg PBW	-1.60 (-4.52 to 1.32), 0.277
Plateau pressure, cmH_2O	-0.92 (-1.71 to -0.14), 0.022
Minute-ventilation, l/min	0.82 (-1.01 to 2.64), 0.372
Laboratory Parameters at the first day	
$PaCO_2$, mmHg	-0.09 (-0.37 to 0.20), 0.544
Lactate, mg/dL	-0.04 (-0.22 to 0.13), 0.616

$ECCO_2R$: extracorporeal carbon dioxide removal; BMI: body mass index; SOFA: sequential organ failure assessment; MV: mechanical ventilation; BPM: breaths per minute; CI: confidence interval; FiO_2: inspired fraction of oxygen; PBW: predicted body weight

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

[a] analysis after multiple imputation

eTable 6 – Multivariable linear regression with ventilator-free days at day 60 as the primary outcome including driving pressure and plateau pressure[a]

	β Coefficient (95% CI), *p*
Age, years	-0.43 (-0.68 to -0.18), 0.001
Gender, male	-2.75 (-14.62 to 9.11), 0.649
BMI, kg/m^2	0.47 (-0.32 to 1.26), 0.243
Risk of death, %*	-0.21 (-0.48 to 0.06), 0.132
SOFA	-1.01 (-3.03 to 1.01), 0.317
Time between MV-$ECCO_2R$	
≤ 24 hours	1 (Reference)
24 – 72 hours	-1.34 (-10.22 to 7.54), 0.767
> 72 hours	-10.13 (-18.44 to -1.82), 0.017
Ventilatory Parameters at the first day	
Tidal volume, ml/kg PBW	-0.97 (-3.80 to 1.86), 0.495
Plateau pressure, cmH_2O	-0.43 (-1.31 to 0.46), 0.344
Driving pressure, cmH_2O	-1.33 (-2.77 to 0.11), 0.070
Minute-ventilation, l/min	0.85 (-1.06 to 2.76), 0.372
Laboratory Parameters at the first day	
$PaCO_2$, mmHg	-0.04 (-0.33 to 0.24), 0.762
Lactate, mg/dL	-0.06 (-0.22 to 0.10), 0.427

$ECCO_2R$: extracorporeal carbon dioxide removal; BMI: body mass index; SOFA: sequential organ failure assessment; MV: mechanical ventilation; BPM: breaths per minute; CI: confidence interval; FiO_2: inspired fraction of oxygen; PBW: predicted body weight

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

[a] analysis after multiple imputation

eTable 7 – Comparison of the three models

	Model 1	Model 2	Model 3
AIC	409.814	404.727	409.406
BIC	433.866	428.779	433.458
Wald (χ^2)			
Plateau pressure	2.864	---	0.754
Driving pressure	---	8.564	6.811

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion
Model 1: Plateau Pressure (without driving pressure)
Model 2: Driving Pressure (without plateau pressure)
Model 3: Plateau pressure and driving pressure

eTable 8 – Univariable and multivariable linear regression assessing factors associated with a change in driving pressure in the first day after $ECCO_2R$ beginning

	Univariable	Multivariable[a]
	β Coefficient (95% CI), p value	**β Coefficient (95% CI), p value**
Age, years	0.03 (-0.09 to 0.15), 0.594	---
Gender, male	1.98 (-2.23 to 6.20), 0.356	---
BMI, kg/m^2	-0.06 (-0.34 to 0.23), 0.689	---
PBW, kg	0.04 (-0.10 to 0.17), 0.587	---
Actual weight, kg	-0.02 (-0.11 to 0.06), 0.606	---
Risk of death, %*	-0.03 (-0.9 to 0.02), 0.223	---
SOFA	-0.10 (-0.48 to 0.29), 0.617	---
LIS	-0.78 (-3.45 to 1.88), 0.556	---
Time between MV-$ECCO_2R$		
≤ 24 hours	1 (Reference)	---
24 – 72 hours	-2.07 (-5.65 to 1.51), 0.257	
> 72 hours	-1.40 (-4.90 to 2.11), 0.435	
Type of ARDS		
Pulmonary	1 (Reference)	---
Extra-pulmonary	1.17 (-1.88 to 4.22), 0.454	
Ventilatory Parameters before $ECCO_2R$		
Tidal volume, ml/kg PBW	-0.41 (-1.17 to 0.35), 0.288	---
PEEP, cmH_2O	0.14 (-0.21 to 0.50), 0.413	---
FiO_2, %	-0.01 (-0.08 to 0.06), 0.792	---
Plateau pressure, cmH_2O	-0.43 (-0.66 to -0.20), 0.001	-0.03 (-0.18 to 0.11), 0.677
Driving pressure, cmH_2O	-0.44 (-0.65 to -0.23), < 0.001	-0.43 (-0.68 to -0.18), 0.001
Respiratory rate, bpm	0.01 (-0.08 to 0.10), 0.787	---
Minute-Ventilation, l/min	-0.04 (-0.24 to 0.17), 0.705	---
Static compliance**	0.06 (0.02 to 0.10), 0.006	-0.01 (-0.05 to 0.02), 0.407
Laboratory Parameters before $ECCO_2R$		
PaO_2/FiO_2, mmHg	0.02 (-0.01 to 0.05), 0.178	-0.00 (-0.01 to 0.01), 0.805
$PaCO_2$, mmHg	0.05 (-0.03 to 0.13), 0.188	0.03 (-0.01 to 0.08), 0.106
pHa	1.05 (-15.14 to 17.23), 0.897	---
Hemodynamics before ECMO		
MAP, mmHg	0.07 (-0.10 to 0.23), 0.405	---
$ECCO_2R$ settings		
Blood flow, l/min	-0.38 (-7.00 to 6.23), 0.909	---
Sweep gas flow, l/min	0.08 (-0.52 to 0.69), 0.776	---

BMI: body mass index; PBW: predicted body weight; SOFA: sequential organ failure assessment; LIS: lung injury score; MV: mechanical ventilation; PEEP: positive end-expiratory pressure; BPM: breaths per minute; MIN: minutes; CI: confidence interval, FiO_2: inspired fraction of oxygen

*: predicted by APACHE II, APACHE III, SAPS II or SAPS III

**: static compliance calculated as tidal volume / plateau pressure *minus* PEEP (ml / cmH_2O)

[a] variables with a $p < 0.2$ in the univariable analysis were included

eFigure 1 – PRISMA-IPD flow diagram