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PaO2/FiO2 Deterioration During Stable Extracorporeal Membrane Oxygenation Associates With Protracted Recovery and Increased Mortality in Severe Acute Respiratory Distress Syndrome

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Sumário

Introdução: Durante a utilização de oxigenação por membrana extracorporal (ECMO), a razão entre a pressão parcial de oxigénio arterial (PaO_2) e a fração inspirada de oxigénio (FiO_2) - ratio PF - reflete a função nativa pulmonar e a oxigenação artificial. Neste estudo, pretendemos avaliar o ratio PF em doentes sob ECMO e a sua associação com os resultados clínicos.

Métodos: Foi realizado um estudo unicêntrico observacional de doentes adultos que foram submetidos a ECMO venovenoso por síndrome de dificuldade respiratória aguda (ARDS).

Resultados: De um total de 81 doentes, em 37 doentes (46%) o ratio PF reduziu-se entre os dias 1 e 7 da terapêutica com ECMO (Ratio PF deterioration [PF-d]; - 37 ± 6.1 mmHg), enquanto que em 44 doentes (54%) o ratio PF melhorou (Ratio PF improved [PFi] 65 ± 10.8 mm Hg). Os doentes que apresentaram deterioração do ratio PF necessitaram de suporte ECMO mais prolongado, mediana 21 dias [intervalo interquartil (IQR)]: 14–35 dias] versus 13 dias [IQR: 10–20 dias], bem como um número maior de dias de ventilação mecânica invasiva (mediana 33 dias [IQR: 24–52 dias] versus 26 dias [IQR: 22–34 dias]), estadia mais longa em unidades de cuidados intensivos (mediana 44 dias [IQR: 32–74 dias] versus 30 dias [IQR: 25–47 dias]) e no hospital (mediana 66 dias [IQR: 39–95 dias] versus 36 dias [IQR: 28–54 dias]). A mortalidade hospitalar foi superior nos doentes com deterioração do ratio PF (48.7% versus 22.7%). A oxigenação extracorporal não explica a variação do ratio PF, uma vez que permaneceu estável no grupo PF-d e diminuiu no grupo PF-i (198 ± 12.7 mL/min versus 171 ± 8.8 mL/min). O ratio PF prévio ao início de ECMO, a utilização de bloqueio e decúbito ventral, bem como as variáveis ventilatórias foram semelhantes entre os grupos. O grupo PF-d apresentava doentes mais velhos (49 ± 2.1 anos versus 41 ± 1.8 anos) e valores mais baixos de Respiratory

Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score (0.57 ± 0.63 versus 2.2 ± 0.52). Utilizando regressão logística, a variação do ratio PF permaneceu um preditor independente de mortalidade, ajustado para a idade e RESP score.

Conclusão: No ARDS, a deterioração do ratio PF durante o suporte estável com ECMO associa-se a recuperação mais lenta e aumento da mortalidade, não explicada pelas características basais do doente, gravidade do ARDS ou tratamento prévio ao início de ECMO.

Palavras-chave: Síndrome de dificuldade respiratória aguda; Oxigenação extracorporal por membrana; mortalidade; PaO2/FiO2

Abstract

Background: During extracorporeal membrane oxygenation (ECMO), arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2; PF ratio reflects native and artificial lung blood oxygenation). In this study we analyzed PF ratio during ECMO support and its association with clinical outcome.

Methods: This was a single-center observational study of adult patients (n=81) undergoing veno-venous ECMO support for severe acute respiratory distress syndrome.

Results: In 37 patients (46%) PF ratio decreased from ECMO-day 1 to ECMO-day 7 (PF ratio deterioration [PFd]; 37 ± 6.1 mm Hg), whereas in 44 patients PF ratio improved (PF-i; 65 ± 10.8 mm Hg). PF-d group required prolonged ECMO (median 21 days [interquartile range (IQR)]:14–35 days] versus 13 days [IQR: 10–20 days]) and invasive mechanical ventilation (median 33 days [IQR: 24–52 days] versus 26 days [IQR: 22–34 days]), longer intensive care unit (median 44 days [IQR: 32–74 days] versus 30 days [IQR: 25–47 days]), and hospital (median 66 days [IQR: 39–95 days] versus 36 days [IQR: 28–54 days]) lengths of stay, with higher hospital mortality rates (48.7% versus 22.7%). ECMO oxygenation did not explain PF ratio variation that remained stable in PF-d and decreased in PF-i (198 ± 12.7 mL/min versus 171 ± 8.8 mL/min). Pre-ECMO PF ratio, neuromuscular blockade, and prone position, as well as ventilatory variables did not differ between groups. The PF-d group was older (49 ± 2.1 years versus 41 ± 1.8 years) and presented lower Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score (0.57 ± 0.63 versus 2.2 ± 0.52). With the use of logistic regression, PF ratio variation remained an independent predictor of hospital mortality after adjusting for age or RESP score.

Conclusions: In severe acute respiratory distress syndrome, PF ratio deterioration during stable ECMO associates with protracted recovery and increased mortality,

not accounted for by patient baseline characteristics, acute respiratory distress syndrome severity, or pre-ECMO management.

Key-words: Acute respiratory distress syndrome; Extracorporeal membrane oxygenation; Mortality; PaO2/FiO2

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Acronym and abbreviature list

ARDS: acute respiratory distress syndrome
ECMO: extracorporeal membrane oxygenation
FiO2: fraction of inspired oxygen
ICU: intensive care unit
IQR: interquartile range
PaO_2: partial pressure of oxygen in arterial blood
PBW: predict body weight
PEEP: Positive end-expiratory pressure
PF (ratio): ratio partial pressure of oxygen in arterial blood to fraction of inspired oxygen
PFd: ratio PF deterioration (group)
PFi: ratio PF improvement (group)
PRESERVE score: PRedicting dEath for SEvere ARDS on VV-ECMO
RESP score: Respiratory Extracorporeal Membrane Oxygenation Survival Prediction
STD: standard deviation
VV: venovenous

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Thesis outline

This document outlines the study that was performed to check our study hypothesis.
The thesis includes eight sections: background, aim, introduction, material and methods, results, discussion, conclusions and future directions.
Background, introduction and aim sections points out the clinical question for this study and from that the aim is stated.
In the Introduction section we present a clinical problem review. The Methods section comprises a detailed description of the methodologies adopted, including study design, studied population, description of the ECMO technique and patient management during extracorporeal support and the description of statistical analysis and ethical approval.
Results section describes patients characteristics, ventilatory parameters previously and during initial ECMO support, gas exchange and ECMO settings before and during initial ECMO support, ECMO related complications and patient clinical outcomes, as well as survival analysis.
The Discussion section presents a critical review of the results, identifying the limitations of the present study.
Conclusion exposes the importance of this study in this field, while future work preclude the importance of continuous research and future directions in this research line.

Scientific results and financial profits

This research line resulted in the publication of two studies:

- Roncon-Albuquerque R Jr, Ferreira-Coimbra J, Vilares-Morgado R, Figueiredo P, Paiva JA. PaO2/FiO2 Deterioration During Stable Extracorporeal Membrane Oxygenation Associates With Protracted Recovery and Increased Mortality in Severe Acute Respiratory Distress Syndrome. Ann Thorac Surg. 2016;102(6):1878-1885. doi:10.1016/j.athoracsur.2016.06.026;

- Roncon-Albuquerque R Jr, Vilares-Morgado R, van der Heijden GJ, Ferreira-Coimbra J, Mergulhão P, Paiva JA. Outcome and Management of Refractory Respiratory Failure With Timely Extracorporeal Membrane Oxygenation: Single-Center Experience With Legionella Pneumonia. J Intensive Care Med. 2019;34(4):344-350. doi:10.1177/0885066617700121.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a resource-intensive technique (1, 2) increasingly used in refractory severe acute respiratory distress syndrome (ARDS) (3, 4). Recently, several scores have been developed to predict mortality in severe acute respiratory failure before ECMO initiation (5-8). Despite the usefulness of these established pre-ECMO risk scores, data is still lacking on variables that could stratify patients after ECMO initiation and therefore assist clinical decision-making during ECMO support. This could be particularly relevant if we take into account that although recent technological advances increased the feasibility, and therefore the prevalence, of long ECMO runs (9, 10), prolonged ECMO support for adult respiratory failure still associates with high mortality (11).

Despite the widespread use of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF-ratio) as a simple index of hypoxemia to diagnose and grade ARDS severity (12), its prognostic utility in patients requiring ECMO support remains unknown. Importantly, in these patients, PF-ratio reflects native lung function as well as artificial lung support. For each hemoglobin concentration, blood oxygenation by modern artificial lungs is mainly determined by ECMO circuit blood flow as well as by the fraction of oxygen in the sweep gas ventilating the artificial lung (13, 14). The type of circuit can also influence blood oxygenation, with blood recirculation in the ECMO circuit constituting a potential limitation for blood oxygenation when a veno-venous (VV-ECMO) configuration is used (15). In severe ARDS patients with residual native lung function undergoing VV-ECMO, cardiac output is also an important determinant of arterial blood oxygenation. In these patients, when cardiac output significantly increases during stable VV-ECMO blood flows (e.g. hyperdynamic septic shock), PF-ratio decreases as a result of a reduction in the ratio between the blood oxygenated by the artificial lung and the patients' venous blood (16, 17). Notwithstanding its multifactorial nature, PF-ratio variations in a

same patient during stable VV-ECMO support may reflect changes in native lung oxygenation with prognostic relevance.

2. Aim

In the present study, we analyzed PF-ratio variation during the first 7 days of VV-ECMO support for adult severe ARDS and its association with ECMO blood oxygenation, respiratory mechanics and clinical outcomes. We hypothesize that PF-ratio deterioration during stable ECMO blood oxygenation would associate with protracted lung recovery and increased mortality.

3. Material and Methods

An observational study of adult patients with severe respiratory failure treated with VV-ECMO for more than 7 days in Hospital S. João (Porto, Portugal) between November 2009 and September 2015 was performed. Patients were divided in two groups in accordance with PF ratio deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support. More specifically, in the PF-d group the PF ratio at ECMO-day 7 compared with the PF ratio at ECMO-day 1 was less than 1, whereas in the PF-i group the PF ratio at ECMO-day 7 compared with PF ratio at ECMO-day 1 was greater than 1. PF ratio for each time point was obtained using the values of PaO2 and FiO2 obtained during the daily circuit monitoring by the ECMO specialist.

Study Population

Hospital S. João is a 1100-bed tertiary university hospital and has the sole ECMO referral center of the north of Portugal, a region with approximately 4 million inhabitants. It has a case volume of 40 to 50 patients per year, being an Extracorporeal Life Support Organization (ELSO) member (Center 227). Specific ECMO data was prospectively collected from a dedicated database from our ECMO Program. Data from clinical records was collected retrospectively.

Consideration of ECMO for respiratory support was based on the presence of severe respiratory failure (Murray score $\geq$3.0 and/or pH $\leq$7.20 under protective ventilation) with sustained clinical deterioration despite optimal conventional treatment. Aggressive mechanical ventilation (plateau pressure $\geq$30 cmH_2O or fraction of inspired oxygen [FiO_2] $\geq$0.8) for more than 7 days, uncontrolled active bleeding or severe comorbidity were used as contraindications for ECMO institution (18).

Technique of Extracorporeal Support

The VV-ECMO circuit consisted of 2 venous cannulae, a centrifugal pump, a membrane oxygenator, and 3/8" connecting tubes. For blood outflow from the patient, a femoral vein was cannulated percutaneously using the Seldinger technique with a 38- or 55-cm-long, 21 Fr. to 29 Fr. heparin-coated cannula (Maquet-Cardiopulmonary-AG, Hirrlingen, Germany). For blood inflow to the patient, a 15-cm-long, 15 Fr. to 19 Fr. heparin coated cannula was used, implanted in the right internal jugular vein.

The membrane oxygenators used (PLS-Quadrox or HLS Set Advanced 7.0 from Maquet-Cardiopulmonary-AG; or HILITE 7000 LT from Medos Medizintechnik AG) are made of polymethylpentene and have a total gas exchange surface of 1.8-1.9 m^2. The centrifugal pumps used were either the Rotaflow, the integrated pump of the HLS Set Advanced 7.0 (both from Maquet-Cardiopulmonary-AG), or the CentriMag (from Thoratec Corporation). For interhospital and intrahospital transport of patients, either special handheld adaptors (ELS System from Maquet-Cardiopulmonary-AG and the CentriMag Compact System Transporter from Thoratec Corporation) or the Cardiohelp system (Maquet-Cardiopulmonary-AG) were used. All systems have an integrated battery backup for intrahospital and interhospital transport. When available, an oxygenator water supply unit was used for thermoregulation (Heater Unit 35; Maquet-Cardiopulmonary-AG) at the bedside. The filling volume of the complete device is between 400 to 500 mL, depending on tubing length. Systemic anticoagulation was maintained using unfractionated heparin to a partial thromboplastin time of 1.5 normal. Sweep gas flow consisted exclusively in pure oxygen with a flow of 1 to 12 L/min. Blood gas analysis was performed using the RAPIDLab 1200 Systems (Siemens, Munich, Germany). Pressures on the ECMO circuit, arterial, pre- and post-membrane blood gas analysis, as well as general laboratories and complete blood coagulation study were monitored daily by the ECMO specialist. Oxygen transfer rate by the ECMO system was calculated daily multiplying the difference between post- and pre-membrane oxygen blood content by ECMO blood flow.

Patient management on ECMO and weaning from extracorporeal support

After cannulation, patient management was optimized to minimize further ventilator-induced lung injury, according to the standards of our ECMO Center. Pressure control ventilation mode was used with a recommendation for 'lung rest' [tidal volume <4 ml/kg predicted body weight (PBW) and plateau

pressure limitation (<25 cmH_2O)] by the ECMO team. For static respiratory system compliance (RSc) calculation, end-inspiratory plateau pressure was measured after 1 second period of no airflow. Recruitment maneuvers and prone position were not routinely performed during ECMO support. Whenever possible, paralysis was withheld, and sedation was reduced to allow spontaneous breathing.

Regarding oxygenation, ECMO blood flow was maximized to reduce FiO_2 <0.6 and maintain hemoglobin saturation >85%. PEEP was maintained >8 cmH_2O to avoid lung atelectasis. If severe hypoxemia (PaO_2 <60 mm Hg) still subsisted, the threshold for red blood cell transfusion was elevated from 7.0 to 9.0 g/dL. The threshold for prophylactic platelet transfusion was 30.000/μL, whereas the targeted post-transfusion goal was 100.000/μL in the presence of active bleeding. Regarding CO_2 removal by the ECMO system, sweep gas flow was progressively increased to allow a normal pH and normal $PaCO_2$.

As native lung function improved, ECMO blood flow and sweep gas flow were progressively reduced to 2.5-3.0 and 1.0 L/min, respectively. Thereafter, sweep gas flow was shut off under FiO_2 <0.5, PEEP <10 cmH_2O and peak inspiratory pressure <27 cmH_2O. If blood gases remained stable, the ECMO system was then removed, and decannulation with skin suture was carried out. An eco-doppler was routinely performed after decannulation to exclude vascular complications.

Data Collection and Statistical Analysis

The Ethics Committee of the Hospital S. João approved the study and waived the requirement for patient consent. Normally distributed data are reported as mean ± standard error of the mean, whereas nonnormally distributed data are reported as median and interquartile range. Comparisons between groups (PF-d versus PF-i) were performed using independent-samples t test (normal distributed data) or Mann-Whitney U test (nonnormal distributed data) for continuous variables, whereas the X^2 test was used for categorical variables. In Tables 2 and 3 comparisons between different time points (pre-ECMO, ECMO-day 1, ECMO-day 3, and ECMO-day 7) were performed using repeated-measures analysis of variance. In Table 5 logistic regression was performed with hospital mortality as outcome and different PF ratios as potential explanatory variables. In Table 6 and Supplemental Table 6 the independence of the association between (PF-d versus PF-i) PF ratio, age, and Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score in clinical outcome was tested using bivariate linear and logistic regression. In

Figure 1, the p value of the Kaplan-Meier curve was calculated by means of the log-rank test. A p value less than .05 was considered statistically significant. For statistical analysis, SPSS 23.0 (SPSS, Inc, Chicago, IL) was used.

4. Results

Baseline Patient Characteristics (Table 1)

During the time frame of the study, 81 adult patients with severe ARDS supported with VV-ECMO for 7 days or more were included. In 44 patients (54.3%) PF-ratios improved in the first 7 days of ECMO support (PF-i), while in 37 patients (45.7%) PF-ratios deteriorated in the same period (PF-d).

Our cohort included mostly relatively young patients without significant co-morbidities, as indicated by low Charlson indexes. Notwithstanding, PF-d patients were older than patients in PF-i group. However, using univariate logistic regression, patient age did not predict hospital mortality (Suppl. Table 1). No significant differences were observed between groups in ARDS etiology nor in the pre-ECMO use of neuromuscular blockade and prone position. Both groups presented similar SAPS II and SOFA scores. However, PF-d group presented lower RESP scores (0.57±0.63) when compared with PF-i group (2.2±0.52).

Ventilatory Parameters Before and During Initial ECMO Support (Table 2)

No significant differences were detected in baseline ventilatory parameters between groups in the last day before ECMO implantation.

ECMO implantation was accompanied by a significant reduction in ventilatory parameters. To ascertain if there was a time/era effect in the ventilatory strategy during ECMO support, a regression analysis of ECMO and ventilation parameters using year of ECMO run as an independent predictor was performed (Suppl. Table 4). We could observe a time/era effect, with PEEP increasing, while tidal volume / PBW as well as plateau pressure decreased during the time frame of the study. The reduction in ventilatory parameters after ECMO initiation was similar in both groups, with no significant differences between groups in ECMO-Day 1 and ECMO-Day 3.

Differently, at the end of the first week of ECMO support (ECMO-Day 7) PF-i group presented lower FiO2, higher tidal volumes (and higher tidal volumes / PBW) as well as increased static RSc, when compared with PF-d group.

Gas Exchange and ECMO Parameters Before and During Initial ECMO support (Table 3)

No significant differences were detected in gas exchange parameters before ECMO implantation between PF-d and PF-i groups.

ECMO support was accompanied by a subsequent improvement in PF-ratio, decrease in PaCO2 and increase in pH in ECMO-Day 1. Gas exchange parameters, blood lactate concentration and ECMO support settings were similar in PF-i and PF-d groups in ECMO-Day 1 and ECMO-Day 3.

In PF-d group, ECMO O2 transfer remained stable between ECMO-Day 1 and ECMO-Day 7, while in PF-i group it decreased.

Table 1: Baseline characteristics of patients requiring ECMO for severe ARDS.

	All	PF-i	PF-d	*p* =
N	81	44 (54.3%)	37 (45.7%)	-
Age (years)	44±1.4	41±1.8	49±2.1	**0.005**
Male	44 (54.3%)	23 (52.3%)	21 (56.8%)	0.69
Charlson Index	0.80±0.123	0.60±0.129	1.03±0.216	0.09
Type of ARDS				
Pulmonary / Non-pulmonary	75 (93%) / 6 (7%)	41 (93%) / 3 (7%)	34 (92%) / 3 (8%)	0.82
Etiology ARDS				
Viral pneumonia	21 (25.9%)	14 (31.8%)	7 (18.9%)	0.19
Bacterial pneumonia	21 (25.9%)	11 (25.0%)	10 (27.0%)	0.84
Lung contusion	7 (8.6%)	2 (4.5%)	5 (13.5%)	0.24
Pneumonia without SPD	6 (7.4%)	3 (6.8%)	3 (8.1%)	0.83
Extra-pulmonary sepsis	5 (6.2%)	3 (6.8%)	2 (5.4%)	0.79
Other	21 (25.9%)	11 (25.0%)	10 (27.0%)	0.84
Pre-ECMO course (days)				
Hospital to ECMO	8.1±1.10	7.7±1.42	8.6±1.77	0.69
IMV to ECMO	5.6±0.61	5.3±0.84	6.1±0.89	0.55
Pre-ECMO management				
NMB	78 (96.3%)	44 (100%)	34 (91.9%)	0.09
Prone position	67 (82.7%)	37 (84.1%)	30 (81.1%)	0.72
ECMO retrieval	54 (66.7%)	30 (68.2%)	24 (64.9%)	0.75
SAPS II	45.7±1.85	43.6±2.38	48.4±2.88	0.20
SOFA	10.8±0.47	10.7±0.55	10.9±0.85	0.77
PF-ratio	72±2.8	71±4.2	72±3.3	0.80
Murray's score	3.2±0.06	3.2±0.08	3.1±0.09	0.32
RESP score	1.5±0.41	2.2±0.52	0.57±0.63	**0.04**

Data is presented as number of cases (%) or mean±STD. ARDS, acute respiratory distress syndrome; IMV, invasive mechanical ventilation; NMB, neuromuscular blockade; PF-d, deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i, improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-ratio, PaO_2/FiO_2; RESP Score, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment score; SPD, specific pathogen detected. SOFA score and PF-ratio were calculated in the last day before ECMO implantation.

Table 2: Ventilatory parameters before and during ECMO support.

	All	PF-i	PF-d
Pre-ECMO			
FiO_2 (%)	95±1.4	97±1.7	93±2.2
PEEP (cmH_2O)	12.0±0.48	11.6±0.74	12.4±0.58
Tidal volume (mL)	470±21	469±37	471±19
Tidal volume / PBW (mL/kg)	7.4±0.31	7.5±0.52	7.3±0.31
Minute ventilation (L/min)	11.1±0.69	11.0±0.92	11.2±1.06
Plateau pressure (cmH_2O)	33.0±0.96	34.4±1.37	31.1±1.2
Static RS compliance (mL/cmH_20)	26.7±2.31	23.5±2.28	30.5±4.16
ECMO Day 1			
FiO_2 (%)	53±2.1[a]	54±3.2[a]	52±2.8[a]
PEEP (cmH_2O)	9.5±0.31[a]	9.6±0.47	9.5±0.41[a]
Tidal volume (mL)	251±13[a]	241±17[a]	263±19[a]
Tidal volume / PBW (mL/kg)	4.2±0.21[a]	4.1±0.31[a]	4.3±0.29[a]
Minute ventilation (L/min)	4.3±0.58[a]	3.6±0.32[a]	5.1±1.24
Plateau pressure (cmH_2O)	25.5±0.43[a]	25.6±0.49[a]	25.5±0.74[a]
Static RS compliance (mL/cmH_20)	17.7±1.07[a]	17.0±1.55[a]	18.4±1.45
ECMO Day 3			
FiO_2 (%)	54±4.2[a]	55±7.6[a]	53±2.9[a]
PEEP (cmH_2O)	9.4±0.31[a]	9.5±0.47	9.2±0.39[a]
Tidal volume (mL)	262±14[a]	264±18[a]	258±20[a]
Tidal volume / PBW (mL/kg)	3.7±0.21[a]	3.5±0.27[a]	4.0±0.31[a]
Minute ventilation (L/min)	3.5±0.23[a]	3.3±0.31[a]	3.7±0.33[a]
Plateau pressure (cmH_2O)	25.8±0.32[a]	25.5±0.46[a]	26.1±0.44[a]
Static RS compliance (mL/cmH_20)	14.6±0.88[a]	13.8±1.16[a]	
ECMO Day 7			
FiO_2 (%)	50±1.8[a]	45±1.9[a,b,c]	56±3.1[a,d]
PEEP (cmH_2O)	8.7±0.31[a,c]	8.8±0.42[a,c]	8.8±0.46[a]
Tidal volume (mL)	285±14[a]	312±19[a]	251±20[a,d]
Tidal volume / PBW (mL/kg)	4.7±0.24[a]	5.2±0.34[a,b]	4.2±0.32[a,d]
Minute ventilation (L/min)	4.6±0.30[a]	4.7±0.36[a]	4.3±0.49[a]

	All	PF-i	PF-d
Plateau pressure (cmH_2O)	25.9±0.40[a]	25.6±0.54[a]	26.2±0.61[a]
Static RS compliance (mL/cmH_20)	18.3±1.29[a]	20.8±1.95	14.9±1.27[a,d]

Data is presented as mean±SEM. FiO_2, fraction of inspired oxygen; PF-d, deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i, improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RS, respiratory system. a, P <.05 vs. Pre-ECMO; b, P <.05 vs. ECMO Day 1; c, P <.05 vs. ECMO Day 3; d, P <.05 vs. PF-i.

Table 3: Gas exchange and ECMO parameters before and during ECMO.

	All	PF-i	PF-d
Pre-ECMO			
PaO_2/FiO_2 (mmHg)	72±2.8	71±4.2	72±3.3
$PaCO_2$ (mmHg)	65±2.7	63±3.1	68±4.7
pH	7.31±0.016	7.32±0.019	7.30±0.027
Lactate (mM)	2.3±0.27	2.1±0.22	2.5±0.56
ECMO Day 1			
PaO_2/FiO_2 (mmHg)	150±6.8[a]	139±9.0[a]	162±10.1[a]
$PaCO_2$ (mmHg)	48±1.3[a]	46±1.7[a]	49±2.1[a]
pH	7.42±0.009[a]	7.44±0.012[a]	7.41±0.014[a]
Lactate (mM)	2.3±0.35	2.0±0.22	2.6±0.71
ECMO blood flow (L/min)	4.4±0.10	4.5±0.15	4.2±0.14
ECMO O_2 transfer (mL/min)	194±8.6	198±12.7	190±11.2
ECMO sweep (L/min)	4.8±0.24	5.1±0.32	4.5±0.35
ECMO Day 3			
PaO_2/FiO_2 (mmHg)	145±6.0[a]	153±8.7[a]	137±7.9[a,b]
$PaCO_2$ (mmHg)	47±1.1[a]	47±1.4[a]	46±1.6[a]
pH	7.40±0.044[a]	7.44±0.008[a]	7.34±0.10[a,b]
Lactate (mM)	1.8±0.15	1.7±0.21[b]	1.9±0.20
ECMO blood flow (L/min)	4.2±0.11	4.2±0.17[b]	4.2±0.15
ECMO O_2 transfer (mL/min)	195±6.0	197±8.0	193±9.3
ECMO sweep (L/min)	5.1±0.26	5.0±0.32	5.2±0.41[b]
ECMO Day 7			
PaO_2/FiO_2 (mmHg)	168±8.6[a,c]	204±12.0[a,b,c]	126±7.7[a,b,c,d]
$PaCO_2$ (mmHg)	47±0.8[a]	46±1.0[a]	47±1.3[a]
pH	7.42±0.008[a]	7.41±0.013[a]	7.44±0.008[a,b]
Lactate (mM)	1.3±0.068[a,c]	1.2±0.10[a,b,c]	1.3±0.085[c]
ECMO blood flow (L/min)	3.9±0.10	3.7±0.14[b,c]	4.3±0.13[d]
ECMO O_2 transfer (mL/min)	178±6.4[c]	171±8.8[b,c]	187±9.1
ECMO sweep (L/min)	4.9±0.25	4.5±0.34	5.4±0.35

Data is presented as mean±SEM. FiO_2, fraction of inspired oxygen; PF-d, deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i, improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PaO_2, partial pressure of oxygen in

arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; Sweep, sweep gas flow; a, P <.05 vs. Pre-ECMO; b, P <.05 vs. ECMO Day 1; c, P <.05 vs. ECMO Day 3; d, P <.05 vs. PF-i.

ECMO-related Complications and ICU Nosocomial Infections (Table 4)
ECMO-related complications were observed in 27.2% of patients, with no significant differences observed between PF-i and PF-d groups. The main ECMO-related complications observed were cannula-associated thrombosis (16.0%), intracerebral hemorrhage (4.9%), ischemic stroke (3.7%) and major bleeding (2.5%). We observed a prevalence of 7.6 cannula-associated thrombosis/1000 cannula days.
Intensive care unit (ICU) nosocomial infections were diagnosed in 60.5% of patients, with no significant differences observed between PF-i and PF-d groups. The most frequent ICU nosocomial infections were ventilator-associated pneumonia (45.7%) and bacteremia (9.9%).

Table 4: Outcome of patients requiring ECMO for severe ARDS.

	All	PF-i	PF-d	*p* =
ECMO-related complications	22 (27.2%)	10 (22.7%)	12 (32.4%)	0.33
Cannula-associated thrombosis	13 (16.0%)	7 (15.9%)	6 (16.2%)	0.97
Intracerebral hemorrhage	4 (4.9%)	1 (2.3%)	3 (8.1%)	0.33
Ischemic stroke	3 (3.7%)	1 (2.3%)	2 (5.4%)	0.59
Major bleeding	2 (2.5%)	1 (2.3%)	1 (2.7%)	0.90
ICU nosocomial infections	48 (59.3%)	25 (56.8%)	23 (62.2%)	0.78
Ventilator-associated pneumonia	37 (45.7%)	18 (40.9%)	19 (51.4%)	0.35
Bacteremia	8 (9.9%)	4 (9.1%)	4 (10.8%)	0.80
Other	3 (3.7%)	3 (6.8%)	0 (0.0%)	0.25
ECMO duration (days)	16 (11-28)	13 (10-20)	21 (14-35)	**0.003**
IMV duration (days)	28 (22-42)	26 (22-34)	33 (24-52)	**0.043**
ICU LOS (days)	37 (25-56)	30 (25-47)	44 (32-74)	**0.033**
Hospital LOS (days)	45 (32-70)	36 (28-54)	66 (39-95)	**0.018**
Tracheostomy in survivors (%)	31 (57.4%)	15 (44.1%)	16 (80.0%)	**0.010**
Hospital mortality (%)	28 (34.6%)	10 (22.7%)	18 (48.7%)	**0.015**

Data is presented as number of cases (%) or median (interquartile range). ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; PF-d, deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i, improvement of PaO_2/FiO_2 in the first 7 days of ECMO support.

PF-ratio and Clinical Outcome

PF-ratio before ECMO implantation, at ECMO-Day 1, at ECMO-Day 3 and at ECMO-Day 7 did not predict hospital mortality (Table 5). Differently, PF-ratio (PF-d vs. PF-i) variation during the first week of ECMO support significantly predicted hospital mortality (Table 5 and Figure 1).

Moreover, PF-d group presented significantly longer duration of ECMO support and invasive mechanical ventilation, higher tracheostomy rate in survivors, as well as longer ICU and hospital length of stay, when compared with PF-i (Table 4).

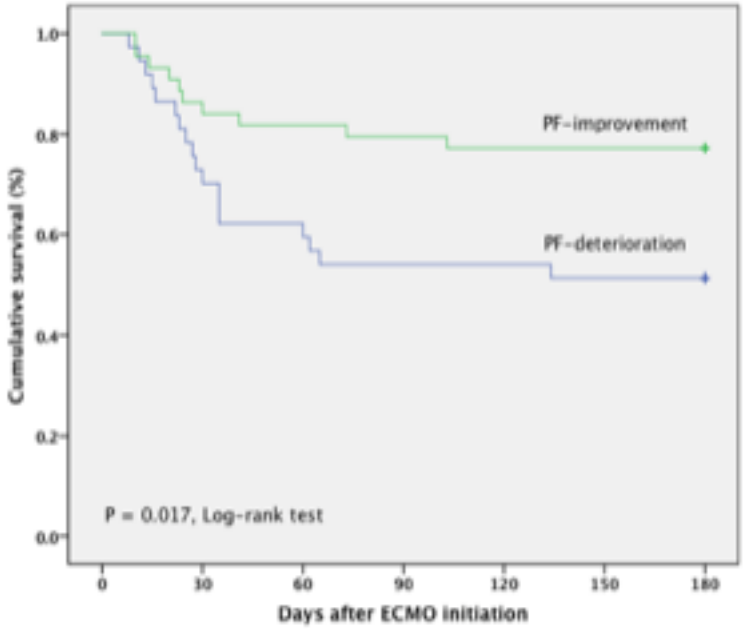
Bivariate regression analysis was performed to test for independence of (PF-i / PF-d) PF-ratio in patient outcome. Given that age is itself a variable included in the RESP score, two different bivariate models were constructed for each clinical outcome variable: Model I with (PF-i / PF-d) PF-ratio and age; and Model II with (PF-i / PF-d) PF-ratio and RESP score. Using both Model I and Model II, clinical outcome could not be accounted by differences in age or RESP score, respectively, while (PF-i / PF-d) PF-ratio remained an independent predictor of clinical outcome (Table 6 and Suppl. Table 6).

Table 5: Univariate logistic regression with hospital mortality as outcome and different PF-ratios as potential explanatory variables.

	OR (95% CI)	*p* =
Hospital Mortality		
PF-ratio: Pre-ECMO	0.99 (0.978 - 1.006)	0.26
PF-ratio: ECMO Day 1	1.00 (0.998 - 1.012)	0.18
PF-ratio: ECMO Day 3	1.00 (0.997 - 1.012)	0.23
PF-ratio: ECMO Day 7	1.01 (0.999 - 1.012)	0.10
(PF-i / PF-d) PF-ratio	3.22 (1.239 - 8.374)	**0.016**

Results are presented as odds ratio (OR) with correspondent 95% confidence intervals. PF-ratio, PaO_2/FiO_2. In (PF-i / PF-d) PF-ratio, patients were divided in two groups in accordance with PaO_2/FiO_2 (PF-ratio) deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support.

Figure 1. Kaplan-Meier cumulative probabilities of survival after ECMO initiation for severe ARDS.



Patients with PaO2/FiO2 improvement during the first 7 days of ECMO support (PF-improvement; green line; n=44) presented higher cumulative survival when compared with patients presenting PaO2/FiO2 deterioration (PF-deterioration; blue line; n=37). The p-value was calculated by means of the log-rank test.

Table 6: Bivariate binary logistic regression models with hospital mortality as outcome.

	OR (95% CI)	***p* =**
Hospital Mortality - Model I		
Age (years)	0.98 (0.944 - 1.024)	0.40
(PF-i / PF-d) PF-ratio	2.83 (1.032 - 7.771)	**0.043**
Hospital Mortality - Model II		
RESP score	1.01 (0.881 - 1.160)	0.88
(PF-i / PF-d) PF-ratio	2.73 (1.009 - 7.386)	**0.048**

Results are presented as odds ratio (OR) with correspondent 95% confidence interval. In (PF-i / PF-d) PF-ratio, patients were divided in two groups in accordance with PaO_2/FiO_2 (PF-ratio) improvement (PF-i) or deterioration (PF-d) in the first 7 days of ECMO support. RESP Score, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.

5. Discussion

In adult severe ARDS requiring ECMO support, PF-ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery and increased mortality.

In our study, PF-ratio at different time points during ECMO support for severe ARDS did not associate with hospital mortality. This could relate to the multifactorial nature of PF-ratio in patients during ECMO support, reflecting blood oxygenation by both native and artificial lungs (13, 14). Accordingly, the increase in PF-ratio observed early after ECMO implantation (pre-ECMO vs. ECMO-Day 1) most probably reflects ECMO blood oxygenation, not native lung function recovery.

Differently, PF-ratio variation during the first week of ECMO support associated with clinical outcome. Patients in PF-d group required prolonged ECMO support and invasive mechanical ventilation, longer ICU and hospital lengths of stay, and presented higher hospital mortality, when compared with PF-i group. PF-ratio variation within the first week of ARDS diagnosis was also found to have prognostic significance in patients treated without ECMO. Bone et al. analyzed PF-ratio and its early response to conventional therapy in the placebo group of a large multicenter study (19). PF-ratio was not different at the time of diagnosis of ARDS in survivors compared to non-survivors. After one day of conventional therapy, including PEEP, those patients who survived increased their PF-ratio, while non-survivors did not improve over a seven-day course. Villar et al. (20) demonstrated that the use of standardized ventilator settings in the first 24 hours after ARDS onset improved PF-ratio in a significant proportion of patients, with 61.3% of patients with severe ARDS to be reclassified as moderate, mild and non-ARDS. Moreover, this ARDS reclassification improved PF-ratio risk stratification.

Importantly, PF-ratio variation in PF-d and PF-i groups could not be accounted by differences in ECMO blood oxygenation. In fact, ECMO O_2 transfer remained stable between ECMO-Day 1 and ECMO-Day 7 in PF-d, while in PF-

i ECMO blood oxygenation even decreased during this period. By comparing PF-ratios of the same patient in different time points that could not be accounted by differences in ECMO blood oxygenation, PF-ratio variation could importantly reflect the initial impact of ECMO treatment on native lung function. In fact, VV-ECMO support allowed a substantial reduction in tidal volume, plateau pressure and fractional inspired oxygen beyond 'conventional' protective ventilation settings, which as been suggested to enhance lung protection in ARDS (21, 22). Accordingly, PF-i group presented improved respiratory system mechanics with higher tidal volumes and improved static RSc at ECMO-Day 7, when compared with PF-d group. These differences in respiratory system mechanics most probably do not relate with differences in lung recruitment, given that PEEP and plateau pressure did not significantly differ between PF-i and PF-d at ECMO-Day 7. Moreover, our results suggest that ventilatory strategies during initial ECMO support that avoid lung atelectasis could improve the outcome of ARDS patients. This goes in line with recent recommendations on mechanical ventilation during ECMO support, underlying the role of higher PEEP levels to avoid atelectasis and associated severe ventilation/perfusion mismatch under low tidal volume and plateau pressure limitation (23). Finally, our results suggest PF-ratio variation during initial ECMO support for severe ARDS as a surrogate end-point to ascertain the potential of any novel therapeutic intervention.

In septic patients undergoing VV-ECMO support, PF-ratio can decrease as a result of a substantial cardiac output increase, that reduces the ratio between the blood oxygenated by the artificial lung and the patients' venous blood (16, 17). Although in the present study cardiac output was not assessed, hyperdynamic septic shock most probably did not explain PF-ratio reduction in PF-d group, given the significant decrease in arterial blood lactate observed between ECMO-Day 1 and ECMO-Day 7.

In our cohort of mostly relatively young adult patients without significant co-morbidities no significant differences were found between PF-d and PF-i groups in most baseline patient characteristics, ARDS etiology, ARDS and ICU severity scores as well as in pre-ECMO management. However, PF-d patients were older when compared to PF-i group. Age has been consistently shown to be an independent predictor of death in ARDS (24, 25) and it has been incorporated in ECMO survival prediction scores for severe acute respiratory failure such as PRESERVE, RESP and the hospital mortality score proposed by Roch et al. (6, 8, 26). This could account, at least in part, to lower RESP scores observed in PF-d group. Importantly, PF-d group presented more than double

hospital mortality when compared with PF-i that could not be anticipated by the observed differences in RESP scores. In fact, when bivariate regression was performed, RESP score could not account for differences in several clinical outcome variables, while PF-ratio variation in the first week of ECMO support remained a predictor of clinical outcome.

We could not observe a significant difference in ECMO-related complications between PF-d and PF-i groups. The prevalence of cannula-associated thrombosis agrees well with the one reported recently by Cooper E et al. (27) in patients with severe respiratory failure following VV-ECMO. Regarding neurologic complications, its occurrence was comparable to that reported in recent studies (28, 29).

In conclusion, in adult patients with severe ARDS, PF-ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery and increased mortality. PF-ratio monitoring could therefore represent a simple tool to stratify patients with severe ARDS during ECMO support.

Limitations of the present study

The present study has a relatively small sample size, which importantly limits its internal and external validity. Moreover, PF-i and PF-d groups are not completely balanced in the indications for ECMO support, which may be impacting survival (and PF-ratio change).

A time/era effect in the mechanical ventilation strategy during ECMO support was also observed, probably reflecting progressively increased compliance to 'lung rest' ventilatory settings during VV-ECMO support in the time frame of the study.

6. **Conclusion**

In conclusion, in adult patients with severe ARDS, PF-ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery and increased mortality. PF-ratio monitoring could therefore represent a simple tool to stratify patients with severe ARDS during ECMO support.

7. Future directions

Survival models had gained importance after the Era of evidence based medicine. However, clinical judgment should not be replaced by survival models as most of prediction models are not precise enough to be the single decision rule.

Meanwhile, in a near future, prediction models using artificial intelligence (AI) algorithms applied to bigger data sets could be used to improve classic modelling. This advances could led to clearly improve prediction in all areas of Medicine, especially in Critical Care Medicine and VV-ECMO, whereas AI can analyze a wide range of variables that are collected in current ICU practice. Following our present research line on VV-ECMO, we will continue to collect patients data in prospective databases to enhance clinical prediction to help clinicians to get the best decision support.

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Appendix

Appendix 1:

Supplementary Tables:

Suppl. Table 1: Univariate logistic regression with hospital mortality as outcome and age, duration of invasive mechanical ventilation and neuromuscular blockade before ECMO implantation, and diagnosis group as potential explanatory variables.

	OR (95% CI)	*p* =
Hospital Mortality		
Age	0.98 (0.942 - 1.008)	0.14
IMV to ECMO	0.93 (0.835 - 1.035)	0.18
NMB	0.17 (0.017 - 1.691)	0.13
Diagnosis group	0.96 (0.784 - 1.176)	0.70

Diagnosis group, acute respiratory diagnosis group according to the classification used in the RESP score; IMV, invasive mechanical ventilation; NMB, neuromuscular blockade; IMV to ECMO, days of IMV before ECMO implantation. The result is presented as odds ratio (OR) with the correspondent 95% confidence interval.

Suppl. Table 2: Univariate linear regression with age as a potential explanatory variable for ventilator parameters.

	R	R Square	B ± SE	*P*
Pre-ECMO				
FiO_2 (%)	0.003	0.000	0.003 ± 0.100	0.98
PEEP (cmH_2O)	0.053	0.003	0.017 ± 0.034	0.62
Tidal volume (mL)	0.126	0.016	1.513 ± 1.435	0.29
Tidal volume / PBW (mL/kg)	0.130	0.017	0.022 ± 0.020	0.28
Minute ventilation (L/min)	0.075	0.006	-0.029 ± 0.048	0.55
Plateau pressure (cmH_2O)	0.329	0.104	-0.203 ± 0.068	**0.004**
Static RS compliance (mL/cmH_20)	0.261	0.068	0.311 ± 0.150	**0.042**
ECMO Day 1				
FiO_2 (%)	0.258	0.066	-0.390 ± 0.150	**0.011**
PEEP (cmH_2O)	0.110	0.012	-0.021 ± 0.021	0.33
Tidal volume (mL)	0.007	0.000	0.061 ± 0.980	0.95
Tidal volume / PBW (mL/kg)	0.109	0.012	0.016 ± 0.015	0.29
Minute ventilation (L/min)	0.063	0.004	0.023 ± 0.038	0.55
Plateau pressure (cmH_2O)	0.189	0.036	-0.049 ± 0.029	0.09
Static RS compliance (mL/cmH_20)	0.174	0.030	0.112 ± 0.073	0.13
ECMO Day 3				
FiO_2 (%)	0.193	0.037	-0.540 ± 0.287	0.06
PEEP (cmH_2O)	0.060	0.004	-0.011 ± 0.021	0.59
Tidal volume (mL)	0.073	0.005	-0.716 ± 1.061	0.50
Tidal volume / PBW (mL/kg)	0.035	0.001	-0.005 ± 0.016	0.74
Minute ventilation (L/min)	0.143	0.020	-0.024 ± 0.017	0.18
Plateau pressure (cmH_2O)	0.090	0.008	-0.021 ± 0.025	0.40
Static RS compliance (mL/cmH_20)	0.021	0.000	-0.014 ± 0.070	0.85
ECMO Day 7				
FiO_2 (%)	0.185	0.034	-0.235 ± 0.138	0.09
PEEP (cmH_2O)	0.139	0.019	-0.026 ± 0.022	0.24
Tidal volume (mL)	0.002	0.000	0.020 ± 1.099	0.99
Tidal volume / PBW (mL/kg)	0.209	0.044	-0.036 ± 0.019	0.06
Minute ventilation (L/min)	0.096	0.009	-0.020 ± 0.023	0.40
Plateau pressure (cmH_2O)	0.128	0.016	-0.034 ± 0.030	0.27
Static RS compliance (mL/cmH_20)	0.154	0.024	-0.130 ± 0.099	0.19

B, unstandardized beta coefficient; FiO_2, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; R, correlation coefficient; RS, respiratory system; SE, standard error.

Suppl. Table 3: Univariate linear regression with age as a potential explanatory variable for gas exchange and ECMO parameters.

	R	R Square	B ± SE	*P*
Pre-ECMO				
PaO_2/FiO_2 (mmHg)	0.042	0.002	-0.106 ± 0.273	0.70
$PaCO_2$ (mmHg)	0.099	0.010	-0.166 ± 0.185	0.37
pH	0.078	0.006	-0.001 ± 0.001	0.47
Lactate (mM)	0.026	0.001	-0.004 ± 0.019	0.81
ECMO Day 1				
PaO_2/FiO_2 (mmHg)	0.281	0.079	1.349 ± 0.486	**0.007**
$PaCO_2$ (mmHg)	0.149	0.022	0.618 ± 0.436	0.16
pH	0.135	0.018	-0.001 ± 0.001	0.21
Lactate (mM)	0.093	0.009	-0.022 ± 0.026	0.40
ECMO blood flow (L/min)	0.035	0.001	- 0.002 ± 0.008	0.75
ECMO O_2 transfer (mL/min)	0.022	0.000	-0.121 ± 0.628	0.85
ECMO sweep (L/min)	0.049	0.002	-0.008 ± 0.018	0.67
ECMO Day 3				
PaO_2/FiO_2 (mmHg)	0.216	0.047	0.952 ± 0.456	**0.040**
$PaCO_2$ (mmHg)	0.014	0.000	-0.010 ± 0.077	0.90
pH	0.052	0.003	-0.001 ± 0.003	0.63
Lactate (mM)	0.095	0.009	-0.009 ± 0.011	0.39
ECMO blood flow (L/min)	0.010	0.000	0.001 ± 0.008	0.93
ECMO O_2 transfer (mL/min)	0.024	0.001	-0.096 ± 0.457	0.83
ECMO sweep (L/min)	0.018	0.000	0.003 ± 0.019	0.87
ECMO Day 7				
PaO_2/FiO_2 (mmHg)	0.013	0.000	0.077 ± 0.683	0.91
$PaCO_2$ (mmHg)	0.051	0.003	0.029 ± 0.066	0.66
pH	0.043	0.002	0.000 ± 0.001	0.71
Lactate (mM)	0.042	0.002	-0.002 ± 0.006	0.72
ECMO blood flow (L/min)	0.129	0.017	0.022 ± 0.029	0.45
ECMO O_2 transfer (mL/min)	0.099	0.010	0.438 ± 0.540	0.42
ECMO sweep (L/min)	0.120	0.014	-0.019 ± 0.018	0.31

B, unstandardized beta coefficient; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; R, correlation coefficient; RS, respiratory system; SE, standard error; Sweep, sweep gas flow.

Suppl. Table 4: Univariate linear regression with year of ECMO run as a potential explanatory variable for ventilator and ECMO parameters.

	R	R Square	B ± SE	*P*
ECMO Day 1				
PEEP (cmH_2O)	0.226	0.051	0.321 ± 0.155	**0.041**
Tidal volume / PBW (mL/kg)	0.027	0.001	-0.029 ± 0.111	0.80
Plateau pressure (cmH_2O)	0.554	0.307	-1.082 ± 0.183	**<0.001**
ECMO blood flow (L/min)	0.288	0.083	0.149 ± 0.055	**0.008**
ECMO Day 3				
PEEP (cmH_2O)	0.211	0.045	0.312 ± 0.156	**0.049**
Tidal volume / PBW (mL/kg)	0.244	0.060	-0.277 ± 0.114	**0.018**
Plateau pressure (cmH_2O)	0.511	0.261	-0.875 ± 0.156	**<0.001**
ECMO blood flow (L/min)	0.323	0.104	0.183 ± 0.057	**0.002**
ECMO Day 7				
PEEP (cmH_2O)	0.212	0.045	0.308 ± 0.166	0.07
Tidal volume / PBW (mL/kg)	0.057	0.003	-0.073 ± 0.143	0.61
Plateau pressure (cmH_2O)	0.487	0.237	-0.967 ± 0.198	**<0.001**
ECMO blood flow (L/min)	0.267	0.071	0.144 ± 0.059	**0.017**

B, unstandardized beta coefficient; FiO_2, fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; R, correlation coefficient; SE, standard error.

Suppl. Table 5: Outcome of survivors requiring ECMO for severe ARDS.

	All	PF-i	PF-d	*p* =
N	53	31 (58.4%)	22 (41.5%)	-
ECMO-related complications	17 (32.1%)	9 (29.0%)	8 (36.4%)	0.86
ICU nosocomial infections	31 (58.5%)	16 (51.6%)	15 (68.2%)	0.31
ECMO duration (days)	14 (10-17)	11 (9-16)	17 (15-30)	**0.014**
IMV duration (days)	25 (19-34)	23 (15-27)	27 (20-53)	0.13
ICU LOS (days)	37 (23-50)	30 (22-38)	52 (27-86)	**0.013**
Hospital LOS (days)	34 (19-57)	25 (17-36)	51 (33-72)	**0.005**
Tracheostomy (%)	31 (57.4%)	15 (44.1%)	16 (80.0%)	**0.010**

Data is presented as number of cases (%) or median (interquartile range). ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; PF-d, deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i, improvement of PaO_2/FiO_2 in the first 7 days of ECMO support.

Suppl. Table 6: Bivariate regression models with different variables as outcome.

	OR or Beta (95% CI)	*p* =
ECMO Days - Model I		
Age (years)	0.002 (-0.406 - 0.414)	0.99
(PF-i / PF-d) PF-ratio	-0.24 (-20.704 - -0.162)	**0.047**
ECMO Days - Model II		
RESP score	0.09 (-0.844 - 1.943)	0.44
(PF-i / PF-d) PF-ratio	-0.280 (-22.514 - -2.298)	**0.017**
IMV Days - Model I		
Age (years)	-0.09 (-0.811 - 0.379)	0.47
(PF-i / PF-d) PF-ratio	-0.31 (-32.948 - -2.863)	**0.020**
IMV Days - Model II		
RESP score	-0.02 (-2.069 - 1.771)	0.88
(PF-i / PF-d) PF-ratio	-0.281 (-30.391 - -2.231)	**0.024**
Tracheostomy in survivors - Model I		
Age (years)	1.01 (0.953 - 1.062)	0.82
(PF-i / PF-d) PF-ratio	5.11 (1.208 - 21.579)	**0.027**
Tracheostomy in survivors - Model II		
RESP score	0.94 (0.787 - 1.117)	0.47
(PF-i / PF-d) PF-ratio	6.43 (1.586 - 26.109)	**0.009**
ICU LOS - Model I		
Age (years)	-0.08 (-1.037 - 0.595)	0.59
(PF-i / PF-d) PF-ratio	-0.41 (-49.885 - -8.072)	**0.008**
ICU LOS - Model II		
RESP score	0.07 (-2.011 - 3.157)	0.66
(PF-i / PF-d) PF-ratio	-0.45 (-52.733 - -10.499)	**0.004**
Hospital LOS - Model I		
Age (years)	-0.27 (-1.769 - 0.051)	0.064
(PF-i / PF-d) PF-ratio	-0.43 (-56.694 - -11.659)	**0.004**
Hospital LOS - Model II		
RESP score	-0.130 (-4.227 - 1.642)	0.38
(PF-i / PF-d) PF-ratio	-0.406 (-56.202 - -9.004)	**0.008**

Results are presented as odds ratio (OR; in logistic regression) or Beta (in linear regression) with correspondent 95% confidence intervals. In (PF-i / PF-d) PF-ratio, patients were divided in two groups in accordance with PaO_2/FiO_2 (PF-ratio) deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support. ICU, intensive care unit; IMV, invasive mechanical ventilation; LOS, length of stay; RESP Score, Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.

Appendix 2:

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PaO_2/FiO_2 Deterioration During Stable Extracorporeal Membrane Oxygenation Associates With Protracted Recovery and Increased Mortality in Severe Acute Respiratory Distress Syndrome

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Background. During extracorporeal membrane oxygenation (ECMO), arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF ratio reflects native and artificial lung blood oxygenation). In this study we analyzed PF ratio during ECMO support and its association with clinical outcome.

Methods. This was a single-center observational study of adult patients (n = 81) undergoing veno-venous ECMO support for severe acute respiratory distress syndrome.

Results. In 37 patients (46%) PF ratio decreased from ECMO-day 1 to ECMO-day 7 (PF ratio deterioration [PF-d]; −37 ± 6.1 mm Hg), whereas in 44 patients PF ratio improved (PF-i; 65 ± 10.8 mm Hg). PF-d group required prolonged ECMO (median 21 days [interquartile range (IQR)]:14–35 days] versus 13 days [IQR: 10–20 days]) and invasive mechanical ventilation (median 33 days [IQR: 24–52 days] versus 26 days [IQR: 22–34 days]), longer intensive care unit (median 44 days [IQR: 32–74 days] versus 30 days [IQR: 25–47 days]), and hospital (median 66 days [IQR: 39–95 days] versus 36 days [IQR: 28–54 days]) lengths of stay, with higher hospital mortality rates (48.7% versus 22.7%). ECMO oxygenation did not explain PF ratio variation that remained stable in PF-d and decreased in PF-i (198 ± 12.7 mL/min versus 171 ± 8.8 mL/min). Pre-ECMO PF ratio, neuromuscular blockade, and prone position, as well as ventilatory variables did not differ between groups. The PF-d group was older (49 ± 2.1 years versus 41 ± 1.8 years) and presented lower Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) scores (0.57 ± 0.63 versus 2.2 ± 0.52). With the use of logistic regression, PF ratio variation remained an independent predictor of hospital mortality after adjusting for age or RESP score.

Conclusions. In severe acute respiratory distress syndrome, PF ratio deterioration during stable ECMO associates with protracted recovery and increased mortality, not accounted for by patient baseline characteristics, acute respiratory distress syndrome severity, or pre-ECMO management.

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Extracorporeal membrane oxygenation (ECMO) is a resource-intensive technique [1, 2], increasingly used in refractory severe acute respiratory distress syndrome (ARDS) [3, 4]. Recently, several scores have been developed to predict mortality in severe acute respiratory failure before ECMO initiation [5–8]. Despite the usefulness of these established pre-ECMO risk scores, data are still lacking on variables that could stratify patients after ECMO initiation and therefore assist clinical decision making during ECMO support. This could be particularly relevant if we take into account that, although recent technologic advances increased the feasibility, and therefore the prevalence, of long ECMO runs [9, 10], prolonged ECMO support for adult respiratory failure still associates with high mortality [11].

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Despite the widespread use of the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF ratio) as a simple index of hypoxemia to diagnose and grade ARDS severity [12], its prognostic utility in patients requiring ECMO support remains unknown. Importantly, in these patients, PF ratio reflects native lung function as well as artificial lung support. For each hemoglobin concentration, blood oxygenation by modern artificial lungs is mainly determined by ECMO circuit blood flow as well as by the fraction of oxygen in the sweep gas ventilating the artificial lung [13, 14]. The type of circuit can also influence blood oxygenation, with blood recirculation in the ECMO circuit constituting a potential limitation for blood oxygenation when a veno-venous ECMO (VV-ECMO) configuration is used [15]. In severe ARDS patients with residual native lung function undergoing VV-ECMO, cardiac output is also an important determinant of arterial blood oxygenation. In these patients, when cardiac output considerably increases during stable VV-ECMO blood flows (eg, hyperdynamic septic shock), PF ratio decreases as a result of a reduction in the ratio between the blood oxygenated by the artificial lung and the patients' venous blood [16, 17]. Notwithstanding its multifactorial nature, PF ratio variations in the same patient during stable VV-ECMO support may reflect changes in native lung oxygenation with prognostic relevance.

In the present study, we analyzed PF ratio variation during the first 7 days of VV-ECMO support for adult severe ARDS and its association with ECMO blood oxygenation, respiratory mechanics, and clinical outcome. We hypothesize that PF ratio deterioration during stable ECMO blood oxygenation would associate with protracted lung recovery and increased mortality.

Patients and Methods

An observational study of adult patients with severe respiratory failure treated with VV-ECMO for more than 7 days in Hospital S. João (Porto, Portugal) between November 2009 and September 2015 was performed.

Patients were divided in two groups in accordance with PF ratio deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support. More specifically, in the PF-d group the PF ratio at ECMO-day 7 compared with the PF ratio at ECMO-day 1 was less than 1, whereas in the PF-i group the PF ratio at ECMO-day 7 compared with PF ratio at ECMO-day 1 was greater than 1. PF ratio for each time point was obtained using the values of PaO_2 and FiO_2 obtained during the daily circuit monitoring by the ECMO specialist.

Study Population and Technique of Extracorporeal Support

A detailed description of the studied population and technique of extracorporeal support, as described previously [18], is provided in the Supplemental Methods section of the Appendix.

Data Collection and Statistical Analysis

The Ethics Committee of the Hospital S. João approved the study and waived the requirement for patient consent. Normally distributed data are reported as mean ± standard error of the mean, whereas nonnormally distributed data are reported as median and interquartile range. Comparisons between groups (PF-d versus PF-i) were performed using independent-samples t test (normal distributed data) or Mann-Whitney U test (non-normal distributed data) for continuous variables, whereas the χ^2 test was used for categorical variables. In Tables 2 and 3 comparisons between different time points (pre-ECMO, ECMO-day 1, ECMO-day 3, and ECMO-day 7) were performed using repeated-measures analysis of variance. In Table 5 logistic regression was performed with hospital mortality as outcome and different PF ratios as potential explanatory variables. In Table 6 and Supplemental Table 6 the independence of the association between (PF-d versus PF-i) PF ratio, age, and Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score in clinical outcome was tested using bivariate linear and logistic regression. In Figure 1, the p value of the Kaplan-Meier curve was calculated by means of the log-rank test. A p value less than .05 was considered statistically significant. For statistical analysis, SPSS 23.0 (SPSS, Inc, Chicago, IL) was used.

Results

Baseline Patient Characteristics

During the time frame of the study, 81 adult patients with severe ARDS supported with VV-ECMO for 7 days or more were included (Table 1). In 44 patients (54.3%) PF ratios improved in the first 7 days of ECMO support (PF-i), whereas in 37 patients (45.7%) PF ratios deteriorated in the same period (PF-d).

Our cohort included mostly relatively young patients without significant comorbidities, as indicated by low Charlson indexes. Notwithstanding, PF-d patients were older than patients in the PF-i group. However, using univariate logistic regression, patient age did not predict hospital mortality (Supplemental Table 1), ventilator parameters (Supplemental Table 2) or gas exchange and ECMO parameters (Supplemental Table 3). No significant differences were observed between groups in ARDS cause or in the pre-ECMO use of neuromuscular blockade and prone position. Both groups presented similar Simplified Acute Physiology II and Sequential Organ Failure Assessment scores. However, the PF-d group presented lower RESP scores (0.57 ± 0.63) compared with the PF-i group (2.2 ± 0.52).

Ventilatory Variables Before and During Initial ECMO Support

No significant differences were detected in baseline ventilatory variables between groups in the last day before ECMO implantation (Table 2).

ECMO implantation was accompanied by a significant reduction in ventilatory variables. To ascertain if there

Table 1. Baseline Characteristics of Patients Requiring ECMO for Severe ARDS

Variable	All	PF-i	PF-d	*p* Value
No. of patients	81	44 (54.3)	37 (45.7)	…
Age, years	44 ± 1.4	41 ± 1.8	49 ± 2.1	0.005
Male sex	44 (54.3)	23 (52.3)	21 (56.8)	0.69
Charlson Index	0.80 ± 0.123	0.60 ± 0.129	1.03 ± 0.216	0.09
Type of ARDS				
Pulmonary/nonpulmonary	75 (93)/6 (7)	41 (93)/3 (7)	34 (92)/3 (8)	0.82
Cause of ARDS				
Viral pneumonia	21 (25.9)	14 (31.8)	7 (18.9)	0.19
Bacterial pneumonia	21 (25.9)	11 (25.0)	10 (27.0)	0.84
Lung contusion	7 (8.6)	2 (4.5)	5 (13.5)	0.24
Pneumonia without SPD	6 (7.4)	3 (6.8)	3 (8.1)	0.83
Extrapulmonary sepsis	5 (6.2)	3 (6.8)	2 (5.4)	0.79
Other	21 (25.9)	11 (25.0)	10 (27.0)	0.84
Pre-ECMO course, days				
Hospital to ECMO	8.1 ± 1.10	7.7 ± 1.42	8.6 ± 1.77	0.69
IMV to ECMO	5.6 ± 0.61	5.3 ± 0.84	6.1 ± 0.89	0.55
Pre-ECMO management				
NMB	78 (96.3)	44 (100)	34 (91.9)	0.09
Prone position	67 (82.7)	37 (84.1)	30 (81.1)	0.72
ECMO retrieval	54 (66.7)	30 (68.2)	24 (64.9)	0.75
SAPS II	45.7 ± 1.85	43.6 ± 2.38	48.4 ± 2.88	0.20
SOFA	10.8 ± 0.47	10.7 ± 0.55	10.9 ± 0.85	0.77
PF ratio	72 ± 2.8	71 ± 4.2	72 ± 3.3	0.80
Murray's score	3.2 ± 0.06	3.2 ± 0.08	3.1 ± 0.09	0.32
RESP score	1.5 ± 0.41	2.2 ± 0.52	0.57 ± 0.63	0.04

Data are presented as number of patients (%) or mean ± standard error of the mean. SOFA score and PF ratio were calculated in the last day before ECMO implantation.

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; IMV = invasive mechanical ventilation; NMB = neuromuscular blockade; PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PF ratio = PaO_2/FiO_2; RESP = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment; SPD = specific pathogen detected.

was a time/era effect in the ventilatory strategy during ECMO support, a regression analysis of ECMO and ventilation variables using year of ECMO as an independent predictor was performed (Supplemental Table 4). We could observe a time/era effect, with positive end-expiratory pressure (PEEP) increasing, whereas tidal volume/predicted body weight (PBW) as well as plateau pressure decreased during the time frame of the study.

The reduction in ventilatory variables after ECMO initiation was similar in both groups, with no significant differences between groups in ECMO-day 1 and ECMO-day 3.

However, at the end of the first week of ECMO support (ECMO-day 7) the PF-i group presented lower FiO_2, higher tidal volumes (and higher tidal volumes/PBW), and increased static RSc (respiratory system compliance), compared with the PF-d group.

Gas Exchange and ECMO Variables Before and During Initial ECMO Support

No significant differences were detected in gas exchange variables before ECMO implantation between the PF-d and PF-i groups (Table 3).

ECMO support was accompanied by a subsequent improvement in PF ratio, decrease in $PaCO_2$, and increase in pH in ECMO-day 1. Gas exchange variables, blood lactate concentration, and ECMO support settings were similar in the PF-i and PF-d groups in ECMO-day 1 and ECMO-day 3.

In the PF-d group, ECMO oxygen transfer remained stable between ECMO-day 1 and ECMO-day 7, whereas it decreased in the PF-i group.

ECMO-Related Complications and ICU Nosocomial Infections

ECMO-related complications were observed in 27.2% of patients, with no significant differences observed between the PF-i and PF-d groups (Table 4 and Supplemental Table 5). The main ECMO-related complications observed were cannula-associated thrombosis (16.0%), intracerebral hemorrhage (4.9%), ischemic stroke (3.7%), and major bleeding (2.5%). We observed a prevalence of 7.6 cannula-associated thrombosis per 1000 cannula days.

Intensive care unit (ICU) nosocomial infections were diagnosed in 60.5% of patients, with no significant differences observed between the PF-i and PF-d groups.

Table 2. Ventilatory Variables Before and During ECMO Support

Variable	All	PF-i	PF-d
Pre-ECMO			
FiO_2, %	95 ± 1.4	97 ± 1.7	93 ± 2.2
PEEP, cm H_2O	12.0 ± 0.48	11.6 ± 0.74	12.4 ± 0.58
Tidal volume, mL	470 ± 21	469 ± 37	471 ± 19
Tidal volume/PBW, mL/kg	7.4 ± 0.31	7.5 ± 0.52	7.3 ± 0.31
Minute ventilation, L/min	11.1 ± 0.69	11.0 ± 0.92	11.2 ± 1.06
Plateau pressure, cm H_2O	33.0 ± 0.96	34.4 ± 1.37	31.1 ± 1.2
Static RS compliance, mL/cm H_2O	26.7 ± 2.31	23.5 ± 2.28	30.5 ± 4.16
ECMO day 1			
FiO_2, %	53 ± 2.1[a]	54 ± 3.2[a]	52 ± 2.8[a]
PEEP, cm H_2O	9.5 ± 0.31[a]	9.6 ± 0.47	9.5 ± 0.41[a]
Tidal volume, mL	251 ± 13[a]	241 ± 17[a]	263 ± 19[a]
Tidal volume/PBW, mL/kg	4.2 ± 0.21[a]	4.1 ± 0.31[a]	4.3 ± 0.29[a]
Minute ventilation, L/min	4.3 ± 0.58[a]	3.6 ± 0.32[a]	5.1 ± 1.24
Plateau pressure, cm H_2O	25.5 ± 0.43[a]	25.6 ± 0.49[a]	25.5 ± 0.74[a]
Static RS compliance, mL/cm H_2O	17.7 ± 1.07[a]	17.0 ± 1.55[a]	18.4 ± 1.45
ECMO day 3			
FiO_2, %	54 ± 4.2[a]	55 ± 7.6[a]	53 ± 2.9[a]
PEEP, cm H_2O	9.4 ± 0.31[a]	9.5 ± 0.47	9.2 ± 0.39[a]
Tidal volume, mL	262 ± 14[a]	264 ± 18[a]	258 ± 20[a]
Tidal volume/PBW, mL/kg	3.7 ± 0.21[a]	3.5 ± 0.27[a]	4.0 ± 0.31[a]
Minute ventilation, L/min	3.5 ± 0.23[a]	3.3 ± 0.31[a]	3.7 ± 0.33[a]
Plateau pressure, cm H_2O	25.8 ± 0.32[a]	25.5 ± 0.46[a]	26.1 ± 0.44[a]
Static RS compliance, mL/cm H_2O	14.6 ± 0.88[a]	13.8 ± 1.16[a]	15.6 ± 1.34[a]
ECMO day 7			
FiO_2, %	50 ± 1.8[a]	45 ± 1.9[a,b,c]	56 ± 3.1[a,d]
PEEP, cm H_2O	8.7 ± 0.31[a,c]	8.8 ± 0.42[a,c]	8.8 ± 0.46[a]
Tidal volume, mL	285 ± 14[a]	312 ± 19[a]	251 ± 20[a,d]
Tidal volume/PBW, mL/kg	4.7 ± 0.24[a]	5.2 ± 0.34[a,b]	4.2 ± 0.32[a,d]
Minute ventilation, L/min	4.6 ± 0.30[a]	4.7 ± 0.36[a]	4.3 ± 0.49[a]
Plateau pressure, cm H_2O	25.9 ± 0.40[a]	25.6 ± 0.54[a]	26.2 ± 0.61[a]
Static RS compliance, mL/cm H_2O	18.3 ± 1.29[a]	20.8 ± 1.95	14.9 ± 1.27[a,d]

[a] $p < .05$ versus pre-ECMO. [b] $p < .05$ versus ECMO day 1. [c] $p < .05$ versus ECMO day 3. [d] $p < .05$ versus PF-i.

Data are presented as mean ± SEM.

ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PaO_2 = arterial oxygen partial pressure; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PBW = predicted body weight; PEEP = positive end-expiratory pressure; RS = respiratory system.

The most frequent ICU nosocomial infections were ventilator-associated pneumonia (45.7%) and bacteremia (9.9%).

PF ratio and Clinical Outcome

PF ratio before ECMO implantation, at ECMO-day 1, at ECMO-day 3 and at ECMO-day 7 did not predict hospital mortality (Table 5). However, PF ratio (PF-d versus PF-i) variation during the first week of ECMO support significantly predicted hospital mortality (Table 5; Fig 1).

Moreover, the PF-d group presented significantly longer duration of ECMO support and invasive mechanical ventilation, higher tracheostomy rate in survivors, and longer ICU and hospital length of stay compared with the PF-I group (Table 4 and Supplemental Table 5).

Bivariate regression analysis was performed to test for independence of (PF-i/PF-d) PF ratio in patient outcome. Given that age is itself a variable included in the RESP score, two different bivariate models were constructed for each clinical outcome variable: model I with (PF-i/PF-d) PF ratio and age and model II with (PF-i/PF-d) PF ratio and RESP score. With the use of both model I and model II, clinical outcome could not be accounted for by differences in age or RESP score, respectively, whereas (PF-i/PF-d) PF ratio remained an independent predictor of clinical outcome (Table 6; Supplemental Table 6).

Comment

In adult severe ARDS requiring ECMO support, PF ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery, and increased mortality.

Table 3. Gas Exchange and ECMO Variables Before and During ECMO

Variable	All	PF-i	PF-d
Pre-ECMO			
PaO_2/FiO_2, mm Hg	72 ± 2.8	71 ± 4.2	72 ± 3.3
$PaCO_2$, mm Hg	65 ± 2.7	63 ± 3.1	68 ± 4.7
pH	7.31 ± 0.016	7.32 ± 0.019	7.30 ± 0.027
Lactate, mmol/L	2.3 ± 0.27	2.1 ± 0.22	2.5 ± 0.56
ECMO day 1			
PaO_2/FiO_2, mm Hg	150 ± 6.8[a]	139 ± 9.0[a]	162 ± 10.1[a]
$PaCO_2$, mm Hg	48 ± 1.3[a]	46 ± 1.7[a]	49 ± 2.1[a]
pH	7.42 ± 0.009[a]	7.44 ± 0.012[a]	7.41 ± 0.014[a]
Lactate, mmol/L	2.3 ± 0.35	2.0 ± 0.22	2.6 ± 0.71
ECMO blood flow, L/min	4.4 ± 0.10	4.5 ± 0.15	4.2 ± 0.14
ECMO O_2 transfer, mL/min	194 ± 8.6	198 ± 12.7	190 ± 11.2
ECMO sweep, L/min	4.8 ± 0.24	5.1 ± 0.32	4.5 ± 0.35
ECMO day 3			
PaO_2/FiO_2, mm Hg	145 ± 6.0[a]	153 ± 8.7[a]	137 ± 7.9[a,b]
$PaCO_2$, mm Hg	47 ± 1.1[a]	47 ± 1.4[a]	46 ± 1.6[a]
pH	7.40 ± 0.044[a]	7.44 ± 0.008[a]	7.34 ± 0.10[a,b]
Lactate, mmol/L	1.8 ± 0.15	1.7 ± 0.21[b]	1.9 ± 0.20
ECMO blood flow, L/min	4.2 ± 0.11	4.2 ± 0.17[b]	4.2 ± 0.15
ECMO O_2 transfer, mL/min	195 ± 6.0	197 ± 8.0	193 ± 9.3
ECMO sweep, L/min	5.1 ± 0.26	5.0 ± 0.32	5.2 ± 0.41[b]
ECMO day 7			
PaO_2/FiO_2, mm Hg	168 ± 8.6[a,c]	204 ± 12.0[a,b,c]	126 ± 7.7[a,b,c,d]
$PaCO_2$, mm Hg	47 ± 0.8[a]	46 ± 1.0[a]	47 ± 1.3[a]
pH	7.42 ± 0.008[a]	7.41 ± 0.013[a]	7.44 ± 0.008[a,b]
Lactate, mmol/L	1.3 ± 0.068[a,c]	1.2 ± 0.10[a,b,c]	1.3 ± 0.085[c]
ECMO blood flow, L/min	3.9 ± 0.10	3.7 ± 0.14[b,c]	4.3 ± 0.13[d]
ECMO O_2 transfer, mL/min	178 ± 6.4[c]	171 ± 8.8[b,c]	187 ± 9.1
ECMO sweep, L/min	4.9 ± 0.25	4.5 ± 0.34	5.4 ± 0.35

[a] $p < .05$ versus pre-ECMO. [b] $p < .05$ versus ECMO day 1. [c] $p < .05$ versus ECMO day 3. [d] $p < .05$ versus PF-i.

Data are presented as mean ± standard error of the mean.

ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; PF-d = deterioration of PaO_2/FiO_2 in the first 7 days of ECMO support; PF-i = improvement of PaO_2/FiO_2 in the first 7 days of ECMO support; PaO_2 = partial pressure of oxygen in arterial blood; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; Sweep = sweep gas flow.

In our study, PF ratio at different time points during ECMO support for severe ARDS did not associate with hospital mortality. This could relate to the multifactorial nature of PF ratio in patients during ECMO support, reflecting blood oxygenation by both native and artificial lungs [13, 14]. Accordingly, the increase in PF ratio observed early after ECMO implantation (pre-ECMO versus ECMO-day 1) most probably reflects ECMO blood oxygenation, not native lung function recovery.

However, PF ratio variation during the first week of ECMO support was associated with clinical outcome. Patients in the PF-d group required prolonged ECMO support and invasive mechanical ventilation, required longer ICU and hospital lengths of stay, and presented higher hospital mortality compared with the PF-i group. PF ratio variation within the first week of ARDS diagnosis was also found to have prognostic significance in patients treated without ECMO. Bone and colleagues [19] analyzed PF ratio and its early response to conventional therapy in the placebo group of a large multicenter study. PF ratio was not different at the time of diagnosis of ARDS in survivors compared with nonsurvivors. After 1 day of conventional therapy, including PEEP, those patients who survived increased their PF ratio, whereas nonsurvivors did not improve over a 7-day course. Villar and colleagues [20] demonstrated that the use of standardized ventilator settings in the first 24 hours after ARDS onset improved PF ratio in a significant proportion of patients, with 61.3% of patients with severe ARDS to be reclassified as moderate, mild, and non-ARDS. Moreover, this ARDS reclassification improved PF ratio risk stratification.

Importantly, PF ratio variation in the PF-d and PF-i groups could not be accounted for by differences in ECMO blood oxygenation. In fact, ECMO oxygen transfer remained stable between ECMO-day 1 and ECMO-day 7 in PF-d, whereas in PF-i ECMO blood oxygenation even decreased during this period. By comparing PF ratios of

Table 4. Outcome of Patients Requiring ECMO for Severe ARDS

Variable	All	PF-i	PF-d	*p* Value
ECMO-related complications	22 (27.2)	10 (22.7)	12 (32.4)	0.33
Cannula-associated thrombosis	13 (16.0)	7 (15.9)	6 (16.2)	0.97
Intracerebral hemorrhage	4 (4.9)	1 (2.3)	3 (8.1)	0.33
Ischemic stroke	3 (3.7)	1 (2.3)	2 (5.4)	0.59
Major bleeding	2 (2.5)	1 (2.3)	1 (2.7)	0.90
ICU nosocomial infections	48 (59.3)	25 (56.8)	23 (62.2)	0.78
Ventilator-associated pneumonia	37 (45.7)	18 (40.9)	19 (51.4)	0.35
Bacteremia	8 (9.9)	4 (9.1)	4 (10.8)	0.80
Other	3 (3.7)	3 (6.8)	0 (0.0)	0.25
ECMO duration, days	16 (11–28)	13 (10–20)	21 (14–35)	0.003
IMV duration, days	28 (22–42)	26 (22–34)	33 (24–52)	0.043
ICU LOS, days	37 (25–56)	30 (25–47)	44 (32–74)	0.033
Hospital LOS, days	45 (32–70)	36 (28–54)	66 (39–95)	0.018
Tracheostomy in survivors, %	31 (57.4)	15 (44.1)	16 (80.0)	0.010
Hospital mortality, %	28 (34.6)	10 (22.7)	18 (48.7)	0.015

Data are presented as number of patients (%) or median (interquartile range).

ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMV = invasive mechanical ventilation; LOS = length of stay; PF-d = deterioration of ratio of arterial oxygen partial pressure to fractional inspired oxygen in the first 7 days of ECMO support; PF-i = improvement of ratio of arterial oxygen partial pressure to fractional inspired oxygen in the first 7 days of ECMO support.

the same patient in different time points that could not be accounted for by differences in ECMO blood oxygenation, PF ratio variation could importantly reflect the initial impact of ECMO treatment on native lung function. In fact, VV-ECMO support allowed a substantial reduction in tidal volume, plateau pressure, and FiO_2 beyond conventional protective ventilation settings, which has been suggested to enhance lung protection in ARDS [21, 22]. Accordingly, the PF-i group presented improved respiratory system mechanics with higher tidal volumes and improved static RSc at ECMO-day 7, compared with the PF-d group. These differences in respiratory system mechanics most probably do not relate with differences in lung recruitment, given that PEEP and plateau pressure did not significantly differ between PF-i and PF-d at ECMO-day 7. Moreover, our results suggest that ventilatory strategies during initial ECMO support that avoid lung atelectasis could improve the outcome of ARDS patients. This goes in line with recent recommendations on mechanical ventilation during ECMO support, underlying the role of higher PEEP levels to avoid atelectasis and associated severe ventilation/perfusion mismatch under low tidal volume and plateau pressure limitation [23]. Finally, our results suggest PF ratio variation during initial ECMO support for severe ARDS as a surrogate end point to ascertain the potential of any novel therapeutic intervention.

In septic patients undergoing VV-ECMO support, PF ratio can decrease as a result of a substantial cardiac output increase that reduces the ratio between the blood oxygenated by the artificial lung and the patients' venous blood [16, 17]. Although in the present study cardiac output was not assessed, hyperdynamic septic shock most probably did not explain PF ratio reduction

Table 5. Univariate Logistic Regression With Hospital Mortality As Outcome and Different PF ratios As Potential Explanatory Variables

Hospital Mortality	OR (95% CI)	*p* Value
PF ratio: pre-ECMO	0.99 (0.978–1.006)	0.26
PF ratio: ECMO day 1	1.00 (0.998–1.012)	0.18
PF ratio: ECMO day 3	1.00 (0.997–1.012)	0.23
PF ratio: ECMO day 7	1.01 (0.999–1.012)	0.10
(PF-i/PF-d) PF ratio	3.22 (1.239–8.374)	0.016

Patients were divided into two groups in accordance with PF ratio deterioration (PF-d) or improvement (PF-i) in the first 7 days of ECMO support.

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; PF ratio = ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Table 6. Bivariate Binary Logistic Regression Models With Hospital Mortality As Outcome

Hospital Mortality	OR (95% CI)	*p* Value
Model I		
Age, years	0.98 (0.944–1.024)	0.40
(PF-i/PF-d) PF ratio	2.83 (1.032–7.771)	0.043
Model II		
RESP score	1.01 (0.881–1.160)	0.88
(PF-i/PF-d) PF ratio	2.73 (1.009–7.386)	0.048

Patients were divided in two groups in accordance with PF ratio improvement (PF-i) or deterioration (PF-d) in the first 7 days of ECMO support.

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; OR = odds ratio; PF ratio = ratio of arterial oxygen partial pressure to fractional inspired oxygen; RESP Score = Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.

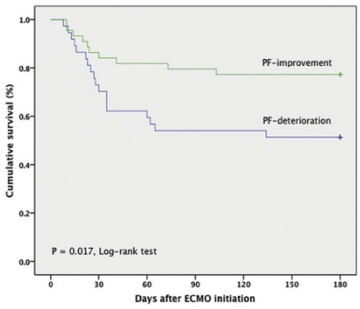

Fig 1. Kaplan-Meier cumulative probabilities of survival after extracorporeal membrane oxygenation (ECMO) initiation for severe acute respiratory distress syndrome. Patients with arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2; PF) improvement during the first 7 days of ECMO support (PF-improvement; green line; n = 44) presented higher cumulative survival compared with patients presenting PaO_2/FiO_2 deterioration (PF-deterioration; blue line; n = 37). The p value was calculated by means of the log-rank test.

in the PF-d group, given the significant decrease in arterial blood lactate observed between ECMO-day 1 and ECMO-day 7.

In our cohort of mostly relatively young adult patients without significant comorbidities no significant differences were found between the PF-d and PF-i groups in most baseline patient characteristics, ARDS cause, ARDS and ICU severity scores, and in pre-ECMO management. However, PF-d patients were older compared with the PF-i group. Age has been consistently shown to be an independent predictor of death in ARDS [24, 25], and it has been incorporated in ECMO survival prediction scores for severe acute respiratory failure such as PRESERVE (Predicting Death for Server ARDS on VV-ECMO), RESP, and the hospital mortality score proposed by Roch and colleagues [6, 8, 26]. This could account, at least in part, to lower RESP scores observed in the PF-d group. Importantly, the PF-d group presented more than double hospital mortality compared with PF-i that could not be anticipated by the observed differences in RESP scores. In fact, when bivariate regression was performed, the RESP score could not account for differences in several clinical outcome variables, whereas PF ratio variation in the first week of ECMO support remained a predictor of clinical outcome.

We could not observe a significant difference in ECMO-related complications between the PF-d and PF-i groups. The prevalence of cannula-associated thrombosis agrees well with the one reported recently by Cooper and colleagues [27] in patients with severe respiratory failure after VV-ECMO. Regarding neurologic complications, its occurrence was comparable with that reported in recent studies [28, 29].

In conclusion, in adult patients with severe ARDS, PF ratio deterioration during stable ECMO blood oxygenation associates with worsening respiratory mechanics, protracted recovery, and increased mortality. PF ratio monitoring could therefore represent a simple tool to stratify patients with severe ARDS during ECMO support.

The present study has a relatively small sample size, which importantly limits its internal and external validity. Moreover, the PF-i and PF-d groups are not completely balanced in the indications for ECMO support, which may be affecting survival (and PF ratio change).

A time/era effect in the mechanical ventilation strategy during ECMO support was also observed, probably reflecting progressively increased compliance to lung rest ventilatory settings during VV-ECMO support in the time frame of the study.

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