Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome: A Multicentre Cohort Study and Propensity-matched Analysis

Marco Giani[1,2], Gennaro Martucci[3], Fabiana Madotto[4], Mirko Belliato[5], Vito Fanelli[6,7] Eugenio Garofalo[8], Clarissa Forlini[1], Alberto Lucchini[2], Giovanna Panarello[3], Nicola Bottino[9], Alberto Zanella[9,10], Francesca Fossi[11], Alfredo Lissoni[9], Nicola Peroni[5], Luca Brazzi[6,7], Giacomo Bellani[1,2], Paolo Navalesi[12,13], Antonio Arcadipane[3], Antonio Pesenti[9,10], Giuseppe Foti[1,2], Giacomo Grasselli[9,10]

1 School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy
2 Department of Emergency and Intensive care, ASST Monza, Monza, Italy
3 Department of Anesthesia and Intensive Care, IRCCS-ISMETT, Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione, Palermo, Italia
4 Value-based Health Care Unit, IRCCS Multimedica, Sesto San Giovanni, Italy
5 UOC Anestesia e Rianimazione 1, IRCCS Policlinico San Matteo, Pavia, Italy
6 Department of Surgical Sciences, University of Turin, Turin, Italy
7 Department of Anaesthesia, Critical Care and Emergency, Città della Salute e della Scienza Hospital, Turin, Italy
8 Intensive Care Unit, Department of Medical and Surgical Sciences, University Hospital Mater Domini, Magna Graecia University, Catanzaro, Italy
9 Department of Anesthesia, Intensive Care and Emergency, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan
10 Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy
11 Department of Anesthesia, Critical Care and Pain Medicine, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy
12 Department of Medicine, University of Padua, Padua, Italy;
13 Anesthesia and Intensive Care Unit, Padua University Hospital, Padua, Italy.

Corresponding Author:
Marco Giani
Orcid ID 0000-0001-8048-2721
Rianimazione generale, ASST Monza
Via Pergolesi 33, 20900 Monza
marco.giani@unimib.it
Mobile +39 339 6645600

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Abstract

Rationale: Prone positioning reduces mortality in severe ARDS patients. To date no evidence supports the use of prone positioning during venovenous extracorporeal oxygenation (ECMO).

Objectives: Aim of the study was to assess feasibility, safety and effect on oxygenation and lung mechanics of prone positioning during ECMO. As a secondary exploratory aim, we assessed the association between PP and hospital mortality.

Methods: We performed a multicenter retrospective cohort study in six italian ECMO centers, including patients managed with prone positioning (PP) during ECMO support (prone group, four centers) and patients managed in the supine position (control group, two centers). Physiological variables were analyzed at 4 time points (supine before PP, start of PP, end of PP, supine after PP). The association between prone positioning and hospital mortality was assessed by multivariate analysis and propensity score matching.

Results: 240 patients were included, 107 in the prone group and 133 in the supine group. Median duration of the 326 pronation cycles was 15 [12-18] hours. Minor reversible complications were reported in 6% of prone positioning maneuvers. Prone positioning improved oxygenation and reduced intrapulmonary shunt. Unadjusted hospital mortality was lower in the prone group (34 vs 50%, p=0.017). After adjusting for covariates, prone positioning remained significantly associated with a reduction of hospital mortality (OR=0.50, 95%CI: 0.29-0.87). 66 propensity score-matched patients were identified in each group. In this matched sample, patients who underwent pronation had higher ECMO duration (16 vs10 days, p-value=0.0344) but lower hospital mortality (30% vs 53%, p=0.0241).

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Conclusion: Prone positioning during ECMO improved oxygenation and was associated with a reduction of hospital mortality.

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In patients with acute respiratory distress syndrome (ARDS), prone positioning (PP) increases end- expiratory lung volume (1), improves ventilation-perfusion matching (2) and reduces the risk of ventilator-induced lung injury (VILI) (3). It has been demonstrated that PP is associated with a significant survival advantage in the more severe ARDS patients (i.e. those with a PaO_2 to FiO_2 ratio of less than 150mmHg) (4). In patients who remain severely hypoxemic, venovenous extracorporeal membrane oxygenation (V-V ECMO) may be required to maintain viable gas exchanges while granting protective or ultra-protective ventilation, thus allowing lung "rest" and reducing the risk of VILI. The combination of PP and ECMO has a sound rationale, however it has been historically limited by the fear of life-threatening complications, such as cannula dislodgement or sudden decrease of extracorporeal blood flow. To date, scarce data (5–11) support the use of prone positioning during ECMO.

We conducted a multicenter retrospective study to evaluate the efficacy and safety of the application of PP in ARDS patients supported with V-V ECMO. As a secondary exploratory aim, we assessed the association of PP and hospital mortality by comparing patients who underwent PP during ECMO (prone group) with patients treated in ECMO centers where PP is not performed (control group).

Methods

The study was approved in July 2019 by the Institutional Ethics Committee of ASST Monza (ref. 3105) and subsequently by the other local Institutional Review Boards. Written informed consent was waived due to the retrospective nature of the study.

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In this multicentre retrospective study, we enrolled patients treated in six Italian ECMO referral centres between January 2014 and December 2018. We included adult patients with diagnosis of ARDS according to Berlin definition(12) and treated with veno-venous ECMO support. In the "prone group", we enrolled consecutive ECMO patients who underwent prone positioning in four centres where PP is routinely performed during extracorporeal support (ASST Monza - Monza; Ospedale Maggiore Policlinico - Milano; ISMETT- Palermo; Azienda Ospedaliera Mater Domini – Catanzaro). In the "control group", we enrolled consecutive patients from two ECMO centres where patients are routinely managed in the supine position, without PP (Fondazione IRCCS Policlinico San Matteo – Pavia; Azienda Ospedaliera Universitaria Città della Salute e della Scienza – Torino).

All ECMO centres belong to the Italian National Network for the Treatment of Acute Respiratory failure (Rete RESPIRA). These centres share indications for ECMO, protocols and techniques. Despite not following a strict ventilatory protocol, common ventilation strategies include ultraprotective ventilation (i.e. tidal volume adjusted to maintain a driving pressure < 10-12 cmH2O and respiratory rate below 20 per minute) and the use of moderate PEEP to maintain a partial lung gas exchange. Details about ventilation protocols for each centre are provided in the Online data supplement.

Data Collection

A retrospective chart review was performed. In both study groups (prone and control), we collected the following parameters at baseline (i.e. before start of ECMO support): age, sex, Body mass Index (BMI), comorbidities, aetiology of ARDS, PaO_2 to FiO_2 ratio, Sequential Organ

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Failure Assessment (SOFA) score, therapies before V-V ECMO support (i.e nitric oxide, prone positioning, renal replacement therapy, duration of mechanical ventilation).

In the "prone group" we also collected: day of ECMO when PP was started, number and duration of PP cycles, complications of PP maneuvers, number of PP cycles interrupted for complications. Complication were classified into major (cardiac arrest or malignant cardiac arrhythmia, extubation, ECMO cannulae displacement) and minor (all other reversible complications). Moreover, for every single PP cycle, four different time points were identified:

1. Supine before PP (one hour before prone positioning);
2. Start PP (one hour after prone positioning);
3. End PP (end of prone positioning period);
4. Supine after PP (one hour after supination).

At each time point, ECMO, respiratory and hemodynamic parameters were collected (see additional details on the online data supplement) .

Finally, we evaluated patient outcomes for each study group: duration of ECMO support, length of stay in the intensive care unit (ICU) and hospital mortality, cause of death.

Statistical Analysis

The demographic and clinical characteristics of the population at the time of enrollment (baseline) were reported through appropriate synthesis measures. The incidence of complications related to the pronation maneuver was described in terms of absolute and relative frequency. The population was described according to the study group (prone, control). Demographic variables, clinical baseline parameters and outcomes (mortality, ECMO duration

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and duration of admission to intensive care) between the two treatment groups were evaluated with the chi-square test for categorical variables, or with the Student's T test or the Mann-Whitney test for continuous variables.

For patients in the prone group, parameters were described at each time point and compared by fitting a linear mixed-effect model to consider the intra-subject measurement correlations. The different time points were considered as the independent variables, whereas patients were considered as random effect.

The association between PP and hospital mortality was evaluated with two different approaches: the first based on logistic multivariable regression models, the second based on a propensity score matching of patients belonging to the two treatments. Details on multivariate analysis and propensity score matching technique are provided in the online data supplement. A significance level of 5% was considered for statistical analysis. Data were collected in an Excel database and analyzed using JMP® 14.0 software (SAS, Cary, NC) and SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 240 patients were enrolled, 107 in the prone group and 133 in the control group. Table 1 shows baseline characteristics and outcomes of the study population.

SOFA score was higher in controls ($p<0.001$). RRT before ECMO was used more frequently in the prone group, the use of nitric oxide before ECMO was higher in controls.

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About one third of patients underwent prone positioning before ECMO. In the prone group, the proportion of patients referred from other centers and retrieved on ECMO was higher.

In patients who underwent prone positioning (prone group), the time from ECMO start to the first PP session was 4 [2-7] days. A total of 326 PP maneuvers were analyzed. Mean duration of the pronation cycles was 15 [12-18] hours. No major complication was recorded. Minor reversible complications were reported in 21 out of 326 prone positioning cycles (6%). 6 procedures (2%) were aborted because of respiratory or hemodynamic instability during prone positioning.

Respiratory and hemodynamic parameters during PP are presented in Figure 1 and Table 3.

The intrapulmonary shunt fraction and the PaO_2/FiO_2 ratio significantly improved during PP, and improvement was maintained after resupination (time point 4 vs 1, $p<0.05$). Static compliance of the respiratory system significantly improved after the PP cycle (time point 4 vs 1, $p<0.05$). Minor differences in hemodynamics were detected: mean pulmonary artery pressure and wedge pressure were slightly higher during prone positioning, whereas heart rate was lower at time points 3 and 4.

Table 4 presents unadjusted outcomes in the two study groups. Hospital mortality was significantly lower in the prone group (34%) compared to the control group (50%, $p=0.017$). Duration of ECMO support and ICU stay were higher in the prone group.

Cause of death did not differ significantly between groups ($p=0.223$). Multiple organ failure / shock was the leading cause of death (54% in the prone group, 71 % in controls). Other

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common causes were treatment discontinuation for irreversible lung damage (26% prone group, 10% controls) and fatal bleeding (14% prone group, 16% controls).

Table E1 (Online data Supplement) shows the univariate logistic analysis for hospital mortality. Covariates significantly associated with mortality were age, hypertension, immunodeficiency, SOFA, duration of mechanical ventilation before ECMO and use of prone positioning.

After adjusting for possible confounders, PP resulted significantly associated with lower hospital mortality (OR=0.50, 95%CI: 0.29-0.87) (Table 5).

Propensity score matching method identified 66 patients with similar characteristics in each group (see Tables S2-3 and Figure S1, Electronic Supplement). In this matched sample, patients who underwent pronation had a lower mortality (30% vs 53%, p-value=0.0241) and a higher duration of ECMO (16 vs10 days, p-value=0.0344) compared with patients in control group (Table 6).

Discussion

The main findings of this multicentre, retrospective cohort study on of the use of PP during VV-ECMO in ARDS patients are as follows:

- In experienced centers, PP during ECMO was safe, with an incidence of minor complications in 6% of PP maneuvers. In a small percentage of maneuvers (2%), early supination was necessary to resolve these complications;

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- PP improved PaO_2/FiO_2 ratio and reduced intrapulmonary shunt, without impairment in hemodynamics;
- Mortality was lower in patients who underwent prone positioning during ECMO compared to ECMO controls, even after adjusting for differences between groups in clinical and demographic parameters;
- Duration of ECMO support was higher in the prone group

To date, our study is the first multicentre study on this topic. Its strengths lie in the combination of physiologic and outcome data and in the thorough statistical analysis aimed at limiting the intrinsic biases of the retrospective design. In particular, the use of propensity score matching analysis should minimize the risk of a selection bias in the use of PP.

To date, PP for severe ARDS is probably the single treatment associated with the greater survival advantage in (13) in critically ill patients. It redistributes mechanical ventilation load, reduces tidal hyperinflation (14) and homogenizes the distribution of transpulmonary pressure (15), thus mitigating the risk of VILI from alveolar overstretching and cyclic atelectasis. Several studies and metanalysis have demonstrated that PP significantly reduces mortality of ARDS patients when applied early in patients with moderate-to-severe patients (i.e. with a PaO2/FiO2 ratio below 150 mmHg) in association with lung-protective ventilation settings, and when PP sessions have a duration of at least 12 hours(16). When patients with severe ARDS present refractory hypoxemia despite optimization of mechanical ventilation settings and use of rescue manoeuvres, ECMO support may be required to improve gas exchange and to decrease the burden of mechanical ventilation on the lung, thus minimizing the risk ventilator-induced lung injury (VILI). Theoretically, the combination of PP and ECMO may further increase

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lung protection. However, despite this strong physiological rationale, literature data on the application of PP during ECMO are scarce and mainly come from small, single-center retrospective studies(17) (18), and limited data are available about benefits of this procedure during ECMO support (5). (5, 11). In our study, hospital mortality in the prone group was similar with that reported in the EOLIA trial(19), where PP was frequently used during ECMO. Hospital mortality in control group was high. This might be also due to the fact that patients had multiple organ failure (i.e. a high SOFA score) before ECMO. An association between prone positioning during ECMO and improved survival was reported for the first time by Guervilly et al(6) in a recent retrospective study on 168 ECMO patients. More recently, two single center studies (7, 20)assessed the association of prone positioning during ECMO with patient outcome, with conflicting results. However, in these three studies patients in the prone group were compared with controls from the same ICUs. Hence, the decision to use PP was based on the clinical judgement of attending physicians, potentially resulting in a high risk of selection bias (i.e. clinicians may have decided to use PP in patients with a highest chance of surviving).

The primary outcome of our study was to assess feasibility and physiological response to PP during ECMO, whereas mortality was a secondary exploratory aim. Our study confirms the association between PP and mortality reduction previously reported by Guervilly and Rilinger, but due to the observational design no conclusions can be drawn on the existence of a causal relationship between the use of PP during ECMO and mortality reduction. At least one large RCT has been designed (ClinicalTrials.gov, ref. NCT04139733) to prospectively address the impact of PP during ECMO on mortality.

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Our study has however several limitations. First, it was retrospective in its design, therefore our findings must be confirmed by prospective controlled studies. Second, despite being the largest study on ECMO patient undergoing PP, the study population was relatively small. Third, as discussed above, despite the application of propensity matching analysis, we cannot definitely exclude a selection bias in patients who underwent PP during ECMO. Fourth, a specific ventilatory strategy was applied (i.e. moderate peep, low tidal volumes, low driving pressure), thus our findings might not be generalizable to centres with very different ventilatory approach. Fifth, matched physiologic data for controls were not available. This may have helped in understanding the difference in outcome between groups. Last, patients were treated in different centers. The italian ECMO centers share indications for ECMO, protocols and techniques. However, we cannot exclude that inhomogeneity in patient treatment may have accounted for differences of patient outcome.

Conclusion

The application of prone positioning in patients with ARDS on V-V ECMO improved oxygenation and was associated with a reduction of hospital mortality. The impact of prone positioning during ECMO on mortality has to be confirmed by prospective studies.

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Figure Legend:

Figure 1. Oxygenation and respiratory mechanics at the different time points. Means and confidence intervals. RS, respiratory system; PaO2, arterial oxygen tension; FiO2, inspiratory oxygen fraction; & $p<0.05$ vs 1 – Supine before PP; # $p<0.05$ vs 2 – Start PP; % $p<0.05$ vs 3 – End PP.

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Table 1. Characteristics of study population stratified by treatment (prone group, control group).

	Prone group n = 107	**Control group n = 133**
Males	73 (68.2)	83 (62.4)
Age, years	48 ± 13	49 ± 13
BMI, kg/m^2	28.5 ± 6.5	28.4 ± 8.1
Cause of ARDS		
Pneumonia	99 (92.5)	121 (91.0)
Other	8 (7.5)	12 (9.0)
PaO_2/FiO_2 before ECMO, mmHg	73 ± 29	76 ± 34
SOFA score	9 ± 3	10 ± 4
Prone positioning before ECMO	34 (31.8)	38 (35.2)
Nitric Oxyde before ECMO	8 (7.5)	20 (9.8)
AKI requiring RRT before ECMO	17 (15.9)	9 (6.8)
Duration of MV before ECMO, days	2 [1-6]	2 [1-6]
Comorbidities		
Hypertension	22 (20.6)	46 (34.6)
Diabetes mellitus	17 (15.9)	17 (12.8)
Immunodeficiency	15 (14.0)	30 (22.6)
Active malignancy	*2 (1.9)*	*9 (6.8)*
Autoimmune disorders	*10 (9.4)*	*16 (12.0)*
Immunosuppression	*7 (6.5)*	*10 (7.5)*
Other chronic diseases	21 (19.6)	27 (20.3)
Asthma-COPD	*7 (6.4)*	*17 (12.78)*
Peripheral vasculopathy	*6 (5.6)*	*4 (3.0)*
Chronic heart failure	*6 (5.6)*	*7 (5.3)*
Chronic renal disease	*4 (3.7)*	*2 (1.5)*
Chronic liver disease	*5 (4.7)*	*6 (4.5)*
Patients referred from other centers	*94 (88)*	*101 (77)*
Patient retrieved on ECMO	*86 (80)*	*72 (59)*

Data are expressed as mean ± SD, median [q1-q3] or absolute frequency (% of the study group). BMI, body mass index; ARDS, acute respiratory distress syndrome; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction; ECMO, extracorporeal membrane oxygenation; SOFA, simplified organ failure assessment; AKI, acute kidney injury; RRT, renal replacement therapy; MV, mechanical ventilation; COPD, chronic obstructive pulmonary disease.

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Table 2. Complications of prone position procedures.

Complication	(N=21)
Desaturation	8 (2.5%)
Bleeding	4 (1.2%)
Decrease of extracorporeal blood flow	4 (1.2%)
Hemodinamic instability	2 (0.6%)
$PaCO_2$ increase	1 (0.3%)
Thigh swelling	1(0.3%)
Face swelling	1 (0.3%)
Vomiting	1 (0.3%)

Data are reported as absolute frequency (% of the prone positioning procedures). $PaCO_2$, carbon dioxide arterial tension.

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Table 3. Respiratory and hemodynamic parameters along the different time points.

	1 – Supine before PP	**2 - Start PP**	**3 - End PP**	**4 – Supine after PP**	**p-value**
Blood Flow	3.8±0.8	3.8±0.8	3.7±0.7 #	3.7±0.7 #	*0.003*
Gas Flow	6.5±2.5	6.5±2.5	6.6±2.5	6.5±2.5	*0.808*
FiO_2 ECMO, %	84±20	82±21	80±22 #	80±23 #	*<0.001*
FiO_2 ventilator, %	62±20	59±18 #	58±19 #	58±19 #	*0.002*
Tidal Volume	232±112	231±117	235±115	244±118 # *	*0.026*
Plateau Pressure	26±3	26±3	26±3	26±3	*0.370*
PEEP	15±3	16±3	16±3	16±3	*0.088*
Driving Pressure	11±3	10±3	10±3	10±3	*0.059*
Cpl,rs, ml/cmH_2O	23±14	24±15	24±15	25±15 #	*0.038*
Respiratory Rate, /min	14±9	14±9	13±7	13±8	*0.038*
PaO_2, mmHg	76±24	79±19	87±41 # *	79±26 %	*<0.001*
$PaCO_2$, mmHg	48±7	48±7	48±7	47±7	*0.146*
pH	7.42±0.05	7.41±0.05	7.41±0.05	7.42±0.05	*0.072*
Pulmonary Shunt, %	56±15	49±16 #	46±16 #*	52±17 #%	*<0.001*
PaO2/FiO2, mmHg	135±61	145±60 #	160±77 *#	147±63 #%	*<0.001*
HR, bpm	95±18	96±17	93±17 *	92±18 #*	*<0.001*
MAP, mmHg	81±50	80±12	79±13	77±12	*0.257*
PAPm, mmHg	30±7	32±6 #	32±7 #	30±7 *%	*<0.001*
WP	14±4	15±4 #	15±4 #	14±4	*0.004*
CO	7.9±1.8	8.0±2.0	7.8±2	7.8±1.7	*0.143*

Data are expressed as mean ± standard deviation. **#** p<0.05 vs. 1- Supine before PP; ***** p<0.05 vs. 2- Start PP; **%** p<0.05 vs. 3- End PP. FiO_2 oxygen fraction; Cpl,rs, compliance of the respiratory system; PEEP, positive end expiratory pressure; PaO2, arterial oxygen tension; PaCO2, arterial carbon dioxide tension; HR, heart rate; MAP, mean arterial pressure; PAPm, mean pulmonary artery pressure; WP, wedge pressure; CO, cardiac output.

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Table 4. Outcomes.

	Prone group **n = 107**	**Control group** **n = 133**	p-value
Duration of ECMO support, days			
All patients	16 [11-30]	10 [6-18]	**<.0001**
Alive on ECMO	14 [10-24]	10 [6-16]	**0.0011**
Length of ICU stay, days			
All patients	35 [21-50]	26 [15-51]	**0.0102**
Alive at ICU discharge	33 [21-48]	30 [19-57]	0.4352
Mortality at hospital discharge, n (%)	36 (34.0)	61 (49.6)	**0.0170**

Data are presented as median [q1-q3] or absolute frequency (% of the study group). ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit;

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Table 5. Demographic and clinical parameters associated to hospital mortality (multivariable logistic model on 226 patients).

	Odds ratio (95% CI)	p-value
Age (year)	1.033 (1.010 - 1.056)	0.0051
Pronation (ref. No)	0.499 (0.285 - 0.872)	0.0147
Length of MV before ECMO (day)	1.067 (1.010 - 1.129)	0.0217

MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

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Table 6. Description of matched sample.

	Prone group (n=66)	Control group (n=66)	Standardized difference
Age, years	47 ± 12	47 ± 14	0.0197
Males	43 (65.1)	44 (66.7)	0.0320
BMI, kg/m^2	27.8 ± 6.8	28.4 ± 6.9	0.0902
ARDS due to pneumonia	60 (90.9)	60 (90.9)	0.0000
PaO_2/FiO_2 ratio, mmHg	74 ± 32	73 ± 27	0.0261
SOFA score	10 ± 3	10 ± 3	0.0137
AKI requiring RRT	3 (4.6)	4 (6.1)	0.0677
Hypertension	14 (21.2)	16 (24.2)	0.0724
Diabetes	6 (9.1)	7 (10.6)	0.0509
Immunodeficiency	13 (19.7)	13 (19.7)	0.0000
Other chronic disease	17 (22.7)	14 (21.2)	0.0366
MV before ECMO, days	2 [1-4]	2 [0-4]	0.0264
Outcomes			
Duration of ECMO, days	16 [11-30]	9.5 [6-16]	**0.0344**
Mortality at hospital discharge†	20 (30.3)	31 (52.54)	**0.0241**

Data are presented as mean ± sd, median [q1-q3] or absolute frequency (% of the study group). † Vital status at hospital discharge was missing for 7 patients in the control group. ° McNemar's test, comparison between prone group and control group accounting for paired data. BMI, body mass index; ARDS, acute respiratory distress syndrome; PaO2, arterial oxygen tension; FiO2, inspiratory oxygen fraction; ECMO: extracorporeal membrane oxygenation; AKI, acute kidney injury; RRT, renal replacement therapy; MV, mechanical ventilation; ICU, intensive care unit.

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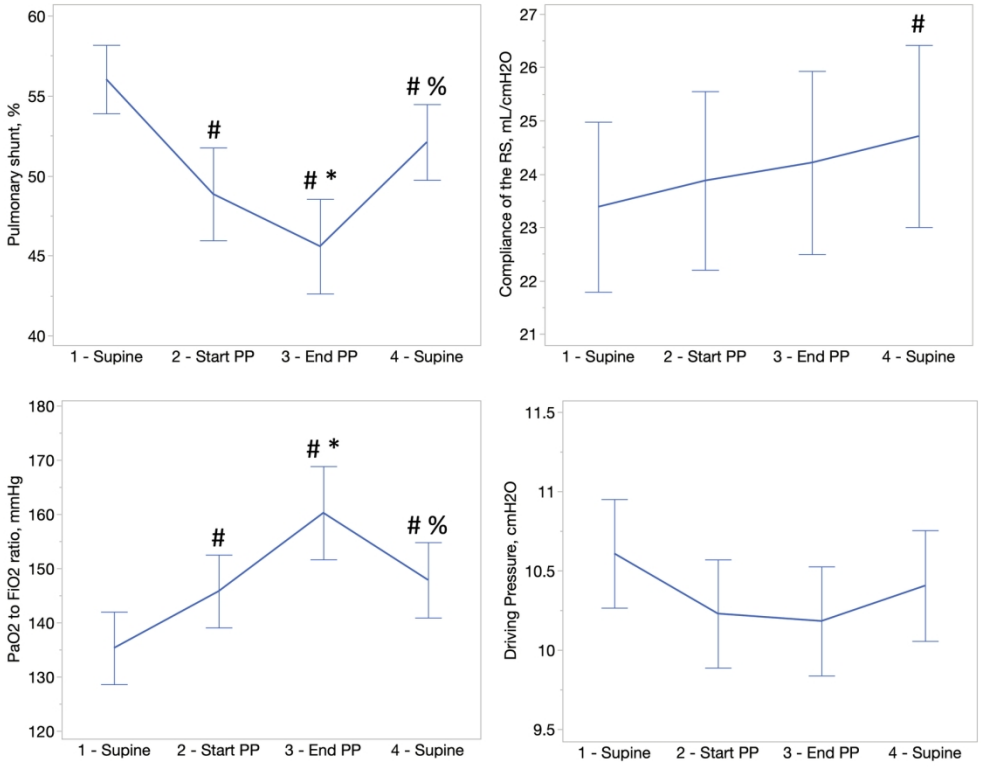

Figure 1. Oxygenation and respiratory mechanics at the different time points. Means and confidence intervals. RS, respiratory system; PaO2, arterial oxygen tension; FiO2, inspiratory oxygen fraction; & p<0.05 vs 1 – Supine before PP; # p<0.05 vs 2 – Start PP; % p<0.05 vs 3 – End PP.

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Online data supplement

Prone Positioning during Venovenous Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome: A Multicentre Cohort Study and Propensity-matched Analysis

Marco Giani, Gennaro Martucci, Fabiana Madotto, Mirko Belliato, Vito Fanelli, Eugenio Garofalo, Clarissa Forlini, Alberto Lucchini, Giovanna Panarello, Nicola Bottino, Alberto Zanella, Francesca Fossi, Alfredo Lissoni, Nicola Peroni, Luca Brazzi, Giacomo Bellani, Paolo Navalesi, Antonio Arcadipane, Antonio Pesenti, Giuseppe Foti, Giacomo Grasselli

METHODS(SUPPLEMENT)

Data Collection

- ECMO V-V parameters: blood flow, gas flow, inspiratory oxygen fraction (FiO_2) at the oxygenator;
- Respiratory system parameters: FiO_2 on the ventilator, tidal volume, respiratory rate, plateau pressure, driving pressure, mean airway pressure, respiratory system compliance, PEEP, driving pressure, respiratory system compliance, arterial oxygen tension (PaO_2), PaO_2 to FiO_2 ratio, intrapulmonary shunt fraction;
- Hemodynamics: heart rate, systolic/mean/diastolic arterial pressure; systolic/mean/diastolic pulmonary arterial pressure, pulmonary artery occlusion (wedge) pressure, cardiac output.

Driving pressure was calculated as plateau pressure minus PEEP, respiratory system compliance as the ratio of tidal volume to driving pressure. Intrapulmonary shunt fraction (calculated according to the Riley equation(12)) and pulmonary hemodynamics parameters were measured in patients with a pulmonary artery catheter.

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Management of mechanical ventilation during ECMO

All centers use ultra-protective mechanical ventilation approach during ECMO. Here we provide the detailed ventilation protocols of each center:

Monza: volume controlled ventilation (VCV), 10 breaths per minute, tidal volume (TV) (<6ml/kg) set to match a DP (driving pressure) of 10 or less, clinical PEEP setting to maintain the lung open while avoiding over-inflation according to oxygenation, best respiratory system compliance (i.e. least driving P for a certain TV) and electrical impedance tomography (EIT)

Milan: VCV or PCV (pressure controlled ventilation), 8 breaths per minute, TV < 6 ml/kg and DP lower than 12 cmH20. PEEP set on oxygenation and best respiratory mechanics

Palermo: PCV, RR 10-15 breaths per min, PEEP 10-14 cmH2O, driving pressure < 10 cmH2O

Catanzaro: VCV, RR 8 breaths per min, PEEP set according to respiratory mechanics and EIT

Turin: VCV, 10 breaths per minute, tidal volume (4-6ml/kg), PEEP set to achieve the lowest driving pressure (10 to 12)

Pavia: VCV or PVC, 8-10 breaths per minute, TV set to maintain a driving pressure below 10-12 (even down to 2-3 ml/kg), PEEP set on P/V curve (usually between 10 and 16cmH2O)

Statistical analysis

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The association between PP and hospital mortality was evaluated with two different approaches: the first based on logistic multivariable regression models, the second based on a propensity score matching of patients belonging to the two treatments.

In the first approach, we identified the independent predictors for hospital mortality through a stepwise regression approach. This approach combines forward and backward selection methods in an iterative procedure (with a significance level of 0.05 both for entry and retention) and possible predictors were represented by demographic and clinical parameters at baseline. Results of the logistic model were reported as odds ratio (OR) with 95% confidence interval (CI).

The second approach was based on propensity score matching method. In detail, the matching algorithm used was the greedy method and patients were matched (1:1 match without replacement) according to the following baseline characteristics: age, sex, body mass index, hypertension, diabetes, immunodeficiency, other chronic diseases, days of mechanical ventilation before ECMO, use of renal replacement therapy (RRT) before ECMO, cause of ARDS, PaO2 to FiO2 ratio, SOFA score. A caliper of 0.2 standard deviation of the logit of the propensity score was used. The similarity of the matched groups was assessed by the standardized differences of each independent variable used in the propensity score estimation. A standardized difference of less 0.10 was considered as indicator of negligible imbalance between groups. Statistical significance of the difference in mortality (at hospital and ICU discharge, during ECMO) was evaluated with McNemar's test. Wilcoxon signed-rank test was used to compare the ECMO duration between matched groups.

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RESULTS (SUPPLEMENT)

Parameter	Beta	SE	Odds ratio (95% CI)	p-value	n
Age (year)	0.029	0.011	1.030 (1.008 - 1.052)	**0.0071**	229
Sex (re. Female)	0.163	0.284	1.177 (0.675 - 2.053)	0.5651	229
BMI (kg/m2)	-0.018	0.019	0.983 (0.947 - 1.020)	0.3566	222
SOFA (score)	0.087	0.038	1.091 (1.013 - 1.174)	**0.0206**	224
Prone positioning before ECMO (ref. No)	-0.649	0.273	0.523 (0.306 - 0.893)	**0.0175**	229
AKI requiring RRT before ECMO (ref. No)	-0.182	0.427	0.833 (0.361 - 1.926)	0.6696	229
Hypertension (ref. No)	0.698	0.293	2.009 (1.131 - 3.568)	**0.0173**	229
Diabetes (ref. No)	0.085	0.375	1.088 (0.522 - 2.268)	0.8213	229
Immunodeficiency (re. No)	0.665	0.336	1.944 (1.007 - 3.756)	**0.0477**	229
Other chronic disease (ref. No)	0.392	0.326	1.479 (0.781 - 2.803)	0.2296	229
Duration of MV before ECMO (day)	0.065	0.028	1.067 (1.011 - 1.126)	**0.0186**	226
PaO2/FiO2 ratio (mmHg)	0.007	0.005	1.007 (0.998 - 1.016)	0.1450	195

Table E1. Hospital mortality. Univariate logistic models. BMI, body mass index; SOFA, simplified organ failure assessment; ECMO, extracorporeal membrane oxygenation; AKI, acute kidney injury; RRT, renal replacement therapy; MV, mechanical ventilation; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction.

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	Prone group (n=107)	***Control group (n=133)***
Age, n (%)	0 (0.00)	0 (0.00)
Sex, n (%)	0 (0.00)	0 (0.00)
BMI, n (%)	0 (0.00)	9 (6.77)
Cause of ARDS, n (%)	0 (0.00)	0 (0.00)
SOFA score, n (%)	2 (1.87)	3 (2.26)
AKI requiring RRT before ECMO*, n (%)*	0 (0.00)	0 (0.00)
Hypertension, n (%)	0 (0.00)	0 (0.00)
Diabetes, n (%)	0 (0.00)	0 (0.00)
Immunodeficiency, n (%)	0 (0.00)	0 (0.00)
Other chronic diseases, n (%)	0 (0.00)	0 (0.00)
Duration of MV before ECMO, n (%)	1 (0.93)	2 (1.50)
PaO2/FiO2 ratio (mmHg)	6 (5.61)	28 (21.05)

Table E2. Variables used for estimating propensity score - number of missing values. BMI, body mass index; ARDS, acute respiratory distress syndrome; SOFA, simplified organ failure assessment; AKI, acute kidney injury; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction.

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	Prone group (n=100)	**Control group (n=95)**	**Standardized difference**
Age, mean ± sd	48.19 ± 11.91	47.91 ± 13.63	0.0222
Males, n (%)	68 (68.00)	62 (65.26)	0.0581
BMI, mean ± sd	28.86 ± 6.51	28.60 ± 8.28	0.0347
ARDS due to pneumonia, n (%)	94 (94.00)	87 (91.58)	0.0937
PaO_2/FiO_2 ratio (mmHg), mean ± sd	72.35 ± 29.19	77.12 ± 34.63	0.1488
SOFA score, mean ± sd	8.51 ± 3.38	10.31 ± 3.58	0.5153
AKI requiring RRT, n (%)	15 (15.00)	4 (4.21)	0.3725
Hypertension, n (%)	21 (21.00)	33 (34.74)	0.3100
Diabetes, n (%)	14 (14.00)	14 (14.74)	0.0210
Immunodeficiency, n (%)	14 (14.00)	22 (23.16)	0.2371
Other chronic diseases, n (%)	20 (20.00)	19 (20.00)	0.0000
Days of mechanical ventilation before ECMO, median [q1-q3]	2.0 [1.0-5.5]	2.0 [1.0-4.0]	0.1207

Table E3. Description of unmatched sample. BMI, body mass index; ARDS, acute respiratory distress syndrome; SOFA, simplified organ failure assessment; AKI, acute kidney injury; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; MV, mechanical ventilation; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction.

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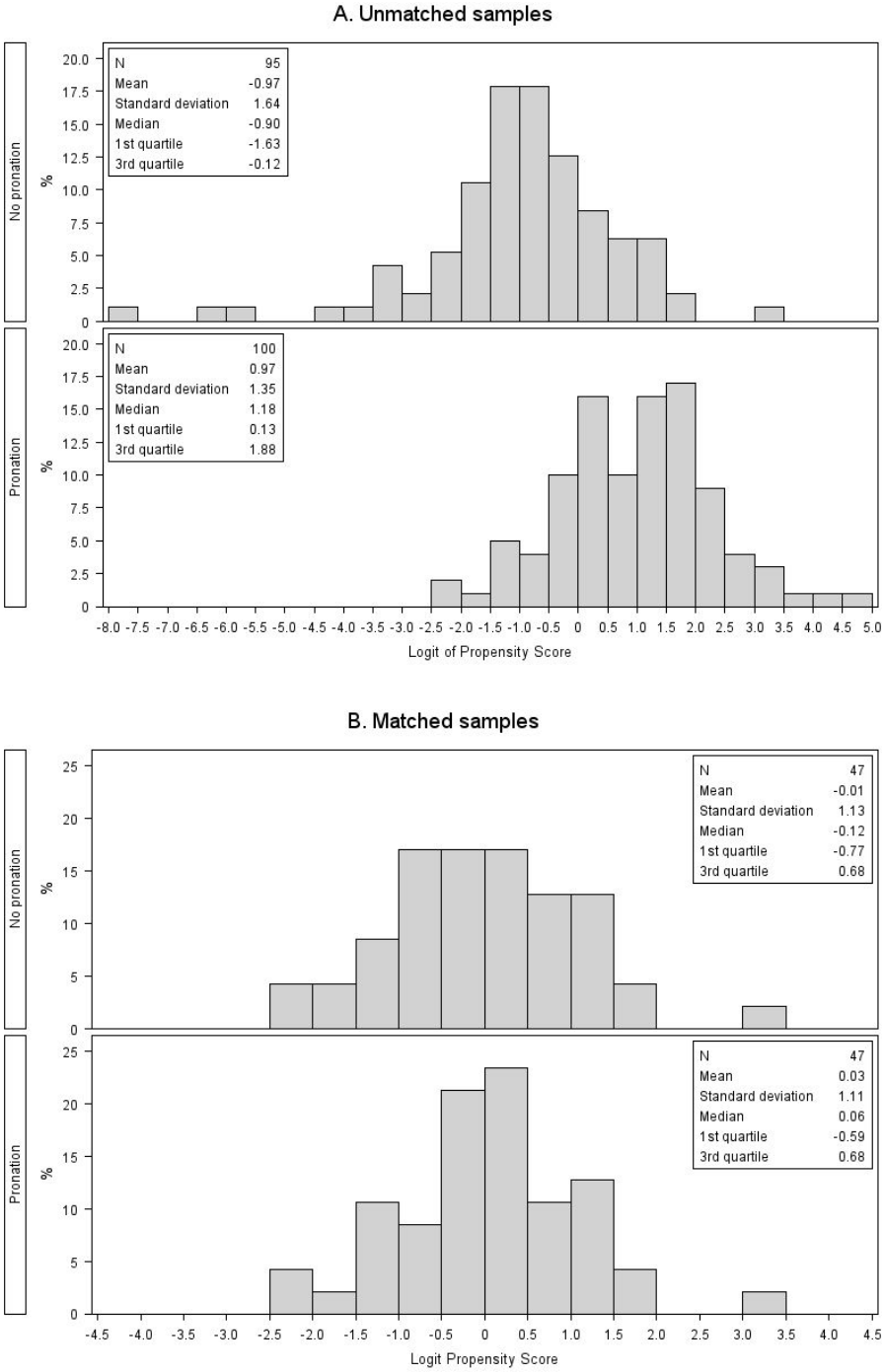

Figure E1. Distribution of logit of propensity score in unmatched (panel A) and matched (panel B) samples.

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