Mechanical Power During Extracorporeal Membrane Oxygenation and Hospital Mortality in Patients With Acute Respiratory Distress Syndrome

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Research

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Abstract

Background: Mechanical power (MP) refers to the energy delivered by a ventilator to the respiratory system per unit of time. MP normalized to predicted body weight (PBW) or respiratory system compliance have better predictive value for mortality than MP alone in acute respiratory distress syndrome (ARDS). Our objective was to assess the potential impact of consecutive changes of normalized MP on hospital mortality among ARDS patients receiving extracorporeal membrane oxygenation (ECMO).

Methods: We performed a secondary analysis of patients with severe ARDS receiving ECMO in a tertiary care referral center in Taiwan between May 2006 and October 2015. Serial changes of MP during ECMO were recorded.

Results: A total of 152 patients with severe ARDS rescued with ECMO were analyzed. Overall hospital mortality was 53.3 %. There were no significant differences between survivors and nonsurvivors in terms of baseline values of MP or other ventilator settings. Cox regression models demonstrated that MP alone, MP normalized to PBW, and MP normalized to compliance during the first 3 days of ECMO were all independently associated with hospital mortality. Higher MP normalized to compliance (HR 2.289 [95% CI 1.214-4.314], $p = 0.010$) was associated with a higher risk of death than MP itself (HR 1.060 [95% CI 1.018-1.104], $p = 0.005$) or MP normalized to PBW (HR 1.004 [95% CI 1.002-1.007], $p < 0.001$). The 90-day hospital mortality of patients with high MP (> 14.4 J/min) during the first 3 days of ECMO was significantly higher than that of patients with low MP (≦ 14.4 J/min) (70.7 % versus 46.8 %, $p = 0.004$), and the 90-day hospital mortality of patients with high MP normalized to compliance (> 0.53 J/min/ml/cm H_2O) during the first 3 days of ECMO was significantly higher than that of patients with low MP normalized to compliance (≦ 0.53 J/min/ml/cm H_2O) (63.1 % versus 29.5 %, $p < 0.001$).

Conclusions: MP during the first 3 days of ECMO was the only ventilator setting independently associated with 90-day hospital mortality, and MP normalized to compliance during ECMO was more predictive for mortality than was MP alone.

Background

Mechanical ventilation remains the cornerstone of management strategies for acute respiratory distress syndrome (ARDS), and extracorporeal membrane oxygenation (ECMO) is widely used as a salvage therapy for refractory hypoxemia in patients with severe ARDS. ECMO allows the lungs to rest and prevents the risk of ventilator-induced lung injury (VILI) by lowering airway pressure, tidal volume (V_T), and FiO_2. However, the optimal ventilation strategies for patients with severe ARDS receiving ECMO have yet to be defined [1, 2].

Mechanical power (MP) refers to the amount of energy per unit of time transmitted to the respiratory system by a mechanical ventilator, as determined by volume, pressure, flow, and respiratory rate (RR). It is therefore reasonable to assume that MP is superior to single ventilator parameter in predicting the risk of VILI [3, 4]. VILI originates from the interaction between the energy load (*i.e.,* MP) and the

pathophysiological characteristics of the lungs (size, homogeneity and recruitability) [4, 5]. Therefore, the same MP may have different impact on respiratory system depending on the applied conditions of lungs, and MP should be normalized at least to the functional lung size in order to accurately reflect the actual amount of energy applied to the lungs [6, 7].

Recent studies have shown that MP is independently associated with in-hospital mortality among critically ill patients [8], and high MP levels have been linked to increased mortality in ARDS patients [9]. However, MP alone does not have better predictive value for patients with ARDS, and it is preferable to normalize MP to predicted body weight (PBW) [6] or respiratory system compliance in terms of well-aerated tissue [7].

ECMO enhanced lung-protective ventilation to mitigate the energy load delivered to the respiratory system (*i.e.,* MP); however, researchers have yet to contrast the influence of MP alone and MP normalized to functional lung size on the mortality in ARDS patients undergoing ECMO. Our objective in this study was to assess the role of serial changes in MP (adjusted for PBW or compliance) on hospital mortality in patients with severe ARDS undergoing ECMO.

Methods

Study design and patients

This study was based on secondary analysis of patients with severe ARDS who had been treated using ECMO between May 2006 and October 2015 at Chang Gung Memorial Hospital (CGMH) in Taiwan. CGMH is a tertiary care referral center with a 3700-bed general ward and 278-bed adult intensive care unit (ICU) with a high volume of venoarterial and venovenous mode ECMO exceeding 100 cases annually. Exclusion criteria were as follows: (1) age < 20 years, (2) malignancies with poor prognosis within 5 years, (3) significant underlying comorbidities or severe multiple organ failure refractory to treatment, and (4) mortality within 3 days after ECMO initiation. The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201600632B0) and waived the need for informed consent.

Definitions

ARDS was defined in accordance with the Berlin criteria [10]. MP was calculated in accordance with the methods [4] based on V_T, RR, peak inspiratory pressure (Ppeak), and driving pressure (ΔP) using the following equation:

MP (Joules/minutes) (J/min) = $0.098 \times V_T \times RR \times (Ppeak - 1/2 \times \Delta P)$.

MP normalized to PBW = MP/PBW.

MP normalized to compliance = MP/Compliance.

Ppeak is equivalent to plateau pressure in pressure-controlled ventilation [11-14]. Ppeak has been used as a surrogate for plateau pressure to calculate MP if not specified [15], and similar effect of MP on mortality was demonstrated when considering Ppeak instead of plateau pressure for calculating MP [8]. One recent prospective study used dynamic driving pressure (Ppeak minus PEEP) to calculate MP, referring to the measure as dynamic MP [16]. Hospital mortality refers to all-cause death during the hospital stay. Patients who remained alive for 90 days after discharge from the hospital were regarded as survivors.

Data collection

Demographic data, risk factors for ARDS, underlying comorbidities, Sequential Organ Failure Assessment (SOFA) score, and lung injury score were collected prior to ECMO initiation. The dates of hospital and ICU admission, ARDS onset, mechanical ventilator initiation and liberation, ECMO cannulation and decannulation, ICU and hospital discharge, and time of death were recorded. Arterial blood gas parameters and mechanical ventilator settings were recorded at the time of ECMO initiation and at approximately 10 a.m. on days 1, 2, and 3 after ECMO initiation.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range), and categorical variables were reported as numbers (percentages). A student's *t* test or the Mann-Whitney *U* test was used to compare continuous variables between groups. Categorical variables were tested using the chi-square test for equal proportions or Fisher's exact test. Paired Student's t tests were used to compare continuous variables before and after ECMO. Receiver operating characteristic curve and Youden index were used to determine the cutoff to dichotomize continuous variables. Risk factors associated with hospital mortality were analyzed using univariate analysis in the first step, followed by Cox proportional hazard regression model with stepwise selection. The results were presented using the hazard ratio (HR) and 95 % confidence interval (CI). Cumulative mortality curves were generated as a function of time using the Kaplan-Meier approach and compared using the log-rank test. All statistical analysis was performed using SPSS 22.0 statistical software, and a two-sided p value < 0.05 was considered statistically significant.

Results

Patients

A total of 152 patients with severe ARDS rescued by ECMO were included in the analysis, which examined the impact of MP on hospital mortality. Overall all-cause in-hospital mortality was 53.3 %. All patients were deeply sedated and paralyzed, and most cases received pressure-controlled ventilation until attempts at weaning from ECMO.

Comparisons of survivors and nonsurvivors

As shown in Table 1, the mean age of nonsurvivors was higher than that of survivors. Nonsurvivors suffered from ARDS for a longer duration before ECMO initiation, and a higher percentage were immunocompromised. There were no significant differences between the two groups in terms of baseline ventilator settings. After receiving ECMO support, nonsurvivors received significantly higher MP than did survivors, with higher MP normalized to PBW, higher MP normalized to compliance, higher Ppeak, lower dynamic compliance, and higher total RR (all $p < 0.05$). The SOFA scores of nonsurvivors were also significantly higher during the first 3 days of ECMO support

Comparing patients receiving high and low mechanical power

As shown in Table 2, the maximum Youden index value was used to categorize patients according to MP, using a cutoff point of 14.4 J/min during the first 3 days of ECMO: high MP group (41 patients; 27 %) and low MP group (111 patients; 73 %). No significant differences were observed between the two groups in terms of MP or other ventilatory variables prior to ECMO initiation. After ECMO support, the high MP and low MP groups differed significantly in all ventilatory parameters except for PEEP and dynamic compliance (all $p < 0.001$). Patients in the high MP group had significantly fewer ventilator-free days on day 60 than did patients in the low MP group, and hospital mortality was significantly higher.

Percentage changes in MP and its components after ECMO and correlation between MP and mortality

Following ECMO initiation, there was a significant reduction in MP among the overall population (49 %, from 23.8 to 12.1 J/min, $p < 0.001$), survivors (55 %, from 24.1 to 10.9 J/min, $p < 0.001$), and nonsurvivors (44 %, from 23.5 to 13.1 J/min, $p < 0.001$). Following ECMO initiation, there was a pronounced decrease in total RR and V_T (33 % and 22 %, respectively, $p < 0.001$) with a less pronounced decrease in Ppeak (6 %) and no change in PEEP in the overall population (Fig. 1). Hospital mortality was correlated with MP during the first 3 days of ECMO but not with the initial MP value before ECMO, and MP higher than 15.0 J/min during the first 3 days of ECMO showed consistently increasing trends in mortality. The hospital mortality was 89 % among patients with MP exceeding 20 J/min during the first 3 days of ECMO and 49.3 % among patients with MP of less than 20 J/min (Fig. 2a and Fig. 2b).

Factors associated with hospital mortality

After adjusting for significant confounding variables, Cox proportional hazard regression models revealed a number of factors that were significantly associated with 90-day hospital mortality: immunocompromised status, ARDS duration before ECMO, SOFA score from days 1-3 on ECMO, MP alone, MP normalized to PBW, and MP normalized to compliance from days 1-3 on ECMO. The risk of death was higher among patients with higher MP normalized to compliance during ECMO compared to those with higher MP alone or higher MP normalized to PBW (HR 2.289, 1.060, and 1.004, respectively, all $p < 0.05$) (Table 3). The overall 90-day survival rate was significantly higher among severe ARDS patients with MP ≦ 14.4 J/min from day 1 to 3 on ECMO than among those with MP > 14.4 J/min (53.2 % versus 29.3 %, $p = 0.004$, log-rank test) (Fig. 3a), and the overall 90-day survival rate was significantly higher among severe ARDS patients with MP normalized to compliance ≦ 0.53 J/min/ml/cm H_2O from day 1 to

3 on ECMO than among those with MP normalized to compliance > 0.53 J/min/ml/cm H_2O (70.5 % versus 36.9 %, $p < 0.001$, log-rank test) (Fig. 3b). MP > 14.4 J/min during the first 3 days of ECMO was independently associated with higher hospital mortality (Adjusted HR 2.340 [95% CI 1.358-4.031]; $p = 0.002$) (Additional file 1: Table S1), and MP normalized to compliance > 0.53 J/min/ml/cm H_2O during the first 3 days of ECMO was independently associated with higher hospital mortality (Adjusted HR 2.238 [95% CI 1.224-4.094]; $p = 0.009$) (Additional file 2: Table S2).

Discussion

This study analyzed consecutive changes in the ventilator settings for patients with severe ARDS receiving ECMO. The primary insight in this research was that MP alone, MP normalized to PBW, and MP normalized to compliance during the first 3 days of ECMO were all independently associated with hospital mortality. Among the ventilator variables, mechanical power normalized to compliance during the first 3 days of ECMO had the greatest predictive value for mortality.

We hypothesized that excessive MP may contribute to the development of VILI and thereby influence clinical outcomes [4]. At the time of this study, there was no clearly defined threshold indicating safe MP values for patients with critical illness or ARDS. One experimental study reported on the development of lung edema and other forms of lung damage when MP exceeded 12 J/min [3]. It has been shown that in-hospital mortality is independently associated with higher MP among critically ill patients, which increases consistently in cases where MP exceeds 17 J/min [8]. In another study using a standardized screening program, 28-day hospital mortality and 3-year mortality were higher in ARDS cases where MP exceeded 22 J/min [9]. However, none of the studies mentioned above considered the effects of changes in MP over time.

ECMO facilitates the use of ultra-protective ventilation, which allows reductions in the contributors of energy load (i.e., MP) to promote lung healing, mitigate further lung injury [1, 2]. Previous studies have reported that during the first 3 days of ECMO, higher PEEP [17] and lower driving pressure [12, 18] were independently associated with lower mortality. However, there was no clearly defined threshold indicating safe ventilator settings and MP values for patients with severe ARDS undergoing ECMO [2].

In the current study, we found that higher MP values during ECMO (but not before ECMO) were associated with increased mortality. We observed a significant difference between patients in the low and high MP groups in terms of mortality but not in terms of baseline MP nor ventilator settings. In a Cox regression models, MP during the first 3 days of ECMO was independently associated with hospital mortality, and the predictive power of MP during ECMO exceeded that of all other individual ventilator variables. MP >14.4 J/min during the first 3 days of ECMO was significantly positively correlated with 90-day hospital mortality and showed greater hazard of death (Adjusted HR, 2.340; 95% CI, 1.358-4.031; $p = 0.002$). Overall, our findings revealed that MP (indicating a conjunction of ventilator settings parameters) during ECMO could be considered a predictor of survival and should be taken into account in optimizing ventilation.

The energy load (MP) delivered to the lungs is not necessarily evenly distributed. The effects of MP on the respiratory system depend not only on the energy load itself but also on the pathophysiology of the lungs (e.g., functional lung size, proportion of inhomogeneity, and the recruitability) [4, 5]. Therefore, MP should be normalized, at least adjusted for functional lung size to reflect the actual amount of energy expected to be delivered to the lungs. Respiratory system compliance is correlated directly with the amount of aerated lung available for tidal ventilation (functional lung size) in patients with ARDS [19]. Zhang *et al.* reported that MP normalized to PBW was far more accurate than the absolute value of MP in predicting mortality [6]. Coppola *et al*. reported no causal relationship between MP alone and mortality, whereas both MP and transpulmonary MP normalized to respiratory system compliance or to the amount of well-aerated tissue were independently associated with ICU mortality [7]. However, the above studies were predicated on baseline MP values, they did not account for serial changes in MP during the ICU stay and did not seek to determine whether the link between MP and mortality was independent from other ventilator settings.

Patients with severe ARDS requiring ECMO tended to have more noninflated tissue (i.e., lower functional lung size), greater inhomogeneity, and greater lung recruitability [20]. There have been relatively few studies examining the effects of MP normalized to functional lung size on mortality in severe ARDS patients receiving ECMO. Cox regression models in our study revealed that the risk of death estimates obtained using MP normalized to compliance were higher than those of MP alone or MP normalized to PBW, despite the fact that all three factors were independently associated with mortality (HR 2.289, 1.060, and 1.004, respectively, all $p < 0.05$). It indicated that functional lung size in ARDS patients is not always proportional to body weight [21], and is generally determined by the severity of the disease and is therefore better quantified by compliance [19]. MP normalized to compliance higher than 0.53 J/min/ml/cm H_2O during the first 3 days on ECMO was significantly associated with greater hazard of death (Adjusted HR, 2.238; 95% CI, 1.224-4.094; $p = 0.009$). Our findings demonstrated that MP normalized to compliance is a superior representation of the actual amount of energy transmitted to the lungs. Precisely defining the safety limits of MP will require further randomized controlled trials to evaluate the correlations between mortality and MP normalized to functional lung size, lung inhomogeneity, and recruitability.

A few studies have examined the effect of RR on VILI and clinical outcomes. Experimental studies have shown that reducing RR ameliorates lung inflammation and lung injury [22] and that the elevated MP resulting from higher RR can induce lung edema and damage [3]. The LUNG SAFE study concluded that increased RR was associated with increased hospital mortality in patients with ARDS [23]. Our study revealed that ECMO had a more pronounced effect on reducing RR than on any other determinants of MP, as mentioned in other recent studies [15, 24, 25]. We also observed that total RR of nonsurvivors was significantly higher than that of survivors during the first 3 days of ECMO.

Besides, the effects of spontaneous breathing could be protective or deleterious, depending on the severity of lung injury and strength of spontaneous activity. This means that lung injury could be worse in cases of severe ARDS, whether receiving ECMO or not, with vigorous spontaneous effort [26]. One recent international study reported mean spontaneous RR of 9 ± 13 breaths/minute before ECMO and 8 ± 11

breaths/minute during the first 2 days of ECMO. This indicated that those patients were not fully sedated and paralyzed, and neuromuscular blocking agents were used in only 41 % of cases [15]. In estimating MP values, patients should be completely relaxed; i.e., without any active inspiratory efforts [7]. In our study, the median spontaneous RR before ECMO was 0 (0-7) breaths/minute and 1 (0-4) breath/minute during the first 3 days of ECMO, indicating that our patients were nearly total sedated and paralyzed. At present, the role of spontaneous effort in patients receiving ECMO for severe ARDS remains unclear, and the benefit or harm were likely depending on the patients' respiratory pattern, patient-ventilator dyssynchrony, pendelluft, and the phase and duration of ARDS [2]. In many cases, implementing a spontaneous breathing ECMO strategy is difficult or clinically infeasible to apply due to the high respiratory drive associated with severe ARDS and the need for deep sedation to mitigate patient self-inflicted lung injury [2, 27, 28].

The most common cause of death among ARDS patients is multiorgan failure [29]. One international multicenter prospective study reported that extrapulmonary organ failure (elevated lactate levels and positive fluid balance) during ECMO had a significantly negative impact on 6-month mortality for patients with ARDS [15]. Our findings revealed that there was no significant difference between survivors and nonsurvivors in terms of MP and SOFA score before ECMO; however, MP and SOFA score were shown to decrease during the first 3 days of ECMO. SOFA score during the first 3 days of ECMO remained independently associated with hospital mortality. These findings indicated that ECMO could facilitate a further reduction in ventilator load (i.e., MP) in order to alleviate VILI by reducing the proinflammatory biotrauma response, thereby preventing multi-organ failure and improving survival [2, 30, 31]. Besides, an immunocompromised status was associated with lower survival, as reported in previous studies in which the 6-month survival rate was only 30 % to 37 % [15, 32]. The timing of ECMO initiation for severe ARDS with refractory hypoxemia has yet to be defined [1]; however, recent studies have also reported a link between ARDS duration before ECMO and mortality [15, 31]. This is perhaps due to the fact that ECMO promotes lung-protective ventilation, such that any delay in initiating ECMO would increase the likelihood of VILI and subsequent mortality.

This study was hindered by a number of limitations. First, this retrospective study was conducted in one tertiary care referral center with a high annual volume of patients requiring ECMO, thereby limiting generalizability. Second, ventilatory variables were recorded only once a day (at approximately 10 a.m.) during the stay in the ICU and therefore do not necessarily represent dynamic changes in ventilator status, including fluctuations in MP during 24-hour intervals. Third, ultra-protective ventilation with V_T below 4 ml/kg PBW has been recommended for patients with ARDS undergoing ECMO [1, 2]. Nonetheless, mean V_T value in the current study was 6 ml/kg PBW after ECMO, due perhaps to the fact that ultra-protective ventilation was not widely implemented between 2006 and 2015. Fourth, we assessed functional lung size by means of PBW and compliance due to the retrospective study, but computed tomography scan of the lungs may be more accurate way to estimate amount of aerated remaining functional lung, lung inhomogeneity or the recruitability [6, 20]. However, computed tomography scan requires intra-hospital patient transfer from ICU to radiology department and the use of ECMO preclude widespread clinical use. Finally, our objective in this observational study was to identify the factors associated with mortality

without considering issues pertaining to causality. Any number of residual or confounding variables that were not measured may have influenced the results.

Conclusions

Our findings revealed that MP, MP normalized to PBW, and MP normalized to compliance during the first 3 days of ECMO were all independently associated with hospital mortality. MP normalized to compliance provided the most predictive value for hospital mortality. Defining safety limits to minimize VILI and decrease mortality in patients with severe ARDS undergoing ECMO may require larger randomized controlled trials to determine whether MP normalized to functional lung size, lung inhomogeneity, or recruitability is causally related to mortality.

Abbreviations

ARDS: acute respiratory distress syndrome; CI: confidence interval; ECMO: extracorporeal membrane oxygenation; HR: hazard ratio; ICU: intensive care unit; MP: mechanical power; PBW: predicted body weight; PEEP: positive end-expiratory pressure; SOFA: sequential organ failure assessment; V_T: tidal volume; Ppeak: peak inspiratory pressure; ΔP: driving pressure; RR: respiratory rate; VILI: ventilator-induced lung injury

Declarations

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Availability of data and materials

The datasets used or analyzed in the study are available from the corresponding author on reasonable request.

Authors' contributions

LCC and KCK assumed responsibility for the accuracy of the data analysis and drafting of the manuscript. LCC, SWL, LPC, HHL, FCT, CHC, and CYH performed the study design and data acquisition. LCC and PHL were responsible for statistical analysis of data. LCC, CSL, SWL, HCH, CCH, HPW, and KCK performed

interpretation of the results. All authors contributed to the completion of the manuscript and have approved the final version.

Ethics approval and consent to participate

The local Institutional Review Board for Human Research approved this study (CGMH IRB No. 201600632B0), and the need for informed consent was waived.

Consent for publication

Not applicable.

Competing interests

On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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Tables

Table 1 Background characteristics and clinical variables: survivors and nonsurvivors

Variables	All	Survivors	Nonsurvivors	
	(n = 152)	(n = 71)	(n = 81)	*p*
Age (years)	50.3 ± 16.4	46.0 ± 16.5	54.1 ± 15.4	0.002
Male (gender)	103 (67.8 %)	48 (67.6 %)	55 (67.9 %)	0.969
Body mass index (kg/m^2)	25.8 ± 5.3	26.0 ± 5.8	25.6 ± 4.7	0.631
ARDS etiologies				
Pulmonary cause	118 (78 %)	59 (83 %)	59 (73 %)	0.130
Extrapulmonary cause	34 (22 %)	12 (17 %)	22 (27 %)	0.130
Diabetes mellitus	40 (26 %)	23 (32 %)	17 (21 %)	0.111
Chronic liver disease	21 (14 %)	6 (9 %)	15 (19 %)	0.073
Immunocompromised status	40 (26 %)	11 (16 %)	29 (36 %)	0.005
SOFA score before ECMO	10.8 ± 3.2	10.3 ± 3.1	11.3 ± 3.2	0.067
Lung injury score before ECMO	3.4 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	0.106
ARDS duration before ECMO (h)	28 (7-122)	10 (4-64)	54 (17-195)	<0.001
PaO_2/FiO_2 (mm Hg) before ECMO	63 (52-88)	64 (53-80)	63 (52-107)	0.168
Ventilator settings before ECMO				
MP (J/min)	23.8 ± 9.6	24.1 ± 10.3	23.5 ± 9.0	0.668
MP/PBW (× 10^{-3}J/min/kg)	416 ± 172	410 ± 174	423 ± 171	0.645
MP/compliance (J/min/ml/cm H_2O)	1.27 ± 0.76	1.21 ± 0.75	1.33 ± 0.78	0.380
Tidal volume (ml/kg PBW)	7.7 ± 2.4	7.7 ± 2.3	7.8 ± 2.5	0.658
PEEP (cmH_2O)	12.0 ± 2.8	12.2 ± 2.5	11.8 ± 3.0	0.288
Peak inspiratory pressure (cm H_2O)	33.9 ± 6.5	33.6 ± 6.0	34.2 ± 6.9	0.605
Mean airway pressure (cm H_2O)	18.6 ± 4.4	18.4 ± 4.2	18.8 ± 4.6	0.588
Dynamic compliance (ml/cm H_2O)	22.6 ± 11.3	23.7 ± 11.6	21.8 ± 11.1	0.420
Total respiratory rate (breaths/min)	24.0 ± 6.9	23.7 ± 7.4	24.3 ± 6.6	0.596
Spontaneous respiratory rate(breaths/min)	0 (0-7)	1 (0-6)	0 (0-7)	0.982
Minute ventilation (L/min)	10.6 ± 3.8	10.7 ± 4.1	10.5 ± 3.6	0.816
SOFA score from day 1 to day 3 on ECMO	9.6 ± 2.3	8.8 ± 1.9	10.4 ± 2.4	<0.001

PaO_2/FiO_2 (mm Hg) from day 1 to day 3 on ECMO	178 (131-240)	200 (146-247)	165 (124-211)	0.588
Ventilator settings from day 1 to day 3 on ECMO				
MP (J/min)	12.1 ± 6.2	10.9 ± 4.3	13.1 ± 7.4	0.022
MP/PBW ($\times 10^{-3}$J/min/kg)	206 ± 111	185 ± 67	226 ± 137	0.022
MP/compliance (J/min/ml/cm H_2O)	0.73 ± 0.46	0.60 ± 0.32	0.86 ± 0.53	<0.001
Tidal volume (ml/kg PBW)	6.0 ± 2.2	6.1 ± 2.0	6.0 ± 2.4	0.914
PEEP (cmH_2O)	12.0 ± 3.3	12.3 ± 3.2	11.7 ± 3.3	0.202
Peak inspiratory pressure (cm H_2O)	31.7 ± 5.6	30.6 ± 5.1	32.8 ± 5.9	0.018
Mean airway pressure (cm H_2O)	17.7 ± 4.0	17.4± 3.6	17.9 ± 4.3	0.406
Dynamic compliance (ml/cm H_2O)	19.2 ± 8.1	21.1 ± 7.7	17.4 ± 8.1	0.006
Total respiratory rate (breaths/min)	16.0 ± 4.4	15.2 ± 4.1	16.7 ± 4.6	0.035
Spontaneous respiratory rate (breaths/min)	1 (0-4)	0 (0-4)	2 (0-5)	0.114
Minute ventilation (L/min)	5.7 ± 2.8	5.2 ± 2.0	6.0 ± 3.2	0.068

Data are presented as mean ± standard deviation, count or median (interquartile range)

ARDS acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *MP* mechanical power, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment

Table 2 Ventilator settings, clinical variables, and outcomes as a function of mechanical power during ECMO

Variables	MP during the first 3 days of ECMO		
	High (n = 41) (> 14.4 J/min)	Low (n = 111) (≤ 14.4 J/min)	*p*
Ventilator settings before ECMO			
MP (J/min)	25.0 ± 9.5	23.3 ± 9.5	0.339
Tidal volume (ml/kg PBW)	8.3 ± 2.3	7.5 ± 2.4	0.062
PEEP (cmH_2O)	11.9 ± 2.7	12.0 ± 2.8	0.786
Peak inspiratory pressure (cm H_2O)	34.4 ± 6.5	33.8 ± 6.5	0.568
Mean airway pressure (cm H_2O)	19.2 ± 3.9	18.4 ± 4.5	0.310
Dynamic compliance (ml/cm H_2O)	22.3 ± 8.4	22.7 ± 12.1	0.869
Total respiratory rate (breaths/min)	23.9 ± 6.7	24.0 ± 7.1	0.891
Spontaneous respiratory rate(breaths/min)	1 (0-6)	0 (0-7)	0.956
Minute ventilation (L/min)	11.2 ± 3.5	10.3 ± 3.9	0.205
Arterial blood gas before ECMO			
pH	7.24 ± 0.16	7.29 ± 0.13	0.056
$PaCO_2$ (mm Hg)	56.1 ± 20.0	51.1 ± 18.4	0.150
PaO_2 (mm Hg)	72.4 ± 33.4	74.5 ± 41.7	0.776
Saturation (%)	83.2 ± 17.4	85.1 ± 14.4	0.508
PaO_2/FiO_2 (mm Hg)	66.5 (49.7-85.7)	63 (53-90.7)	0.882
SOFA score before ECMO	11.9 ± 3.1	10.4 ± 3.1	0.013
Ventilator settings from day 1 to day 3 on ECMO			
MP (J/min)	20.3 ± 5.3	9.1 ± 3.0	<0.001
Tidal volume (ml/kg PBW)	7.4 ± 2.2	5.6 ± 2.0	<0.001
PEEP (cmH_2O)	11.8 ± 2.5	12.0 ± 3.5	0.653
Peak inspiratory pressure (cm H_2O)	35.2 ± 5.4	30.5 ± 5.1	<0.001
Mean airway pressure (cm H_2O)	19.6 ± 3.8	17.0 ± 3.8	<0.001
Dynamic compliance (ml/cm H_2O)	19.9 ± 6.5	18.9 ± 8.5	0.520
Total respiratory rate (breaths/min)	20.3 ± 5.4	14.4 ± 3.5	<0.001

Spontaneous respiratory rate(breaths/min)	4 (1-9)	0 (0-3)	<0.001
Minute ventilation (L/min)	8.9 ± 2.5	4.5 ± 1.6	<0.001
Arterial blood gas from day 1 to day 3 on ECMO			
pH	7.42 ± 0.08	7.44 ± 0.08	0.286
$PaCO_2$ (mm Hg)	38.6 ± 6.5	38.1± 4.7	0.639
PaO_2 (mm Hg)	102.2 ± 65.9	96.1 ± 39.5	0.489
Saturation (%)	94.8 ± 3.3	95.5 ± 2.9	0.240
PaO_2/FiO_2 (mm Hg)	151 (123-212)	189 (140-242)	0.921
SOFA score from day 1 to day 3 on ECMO	10.7 ± 2.2	9.2 ± 2.2	0.001
ECMO complications, n (%)	9 (22 %)	34 (30.6 %)	0.292
Duration of ECMO (days)	7.7 (4.7-11.5)	9.9 (5.9-15.8)	0.287
Duration of mechanical ventilator (days)	15.4 (11.8-34)	22.9 (12.4-39.8)	0.291
Length of ICU stay (days)	19 (10-43)	27 (16-43)	0.182
Length of hospital stay (days)	29 (13-63)	41 (24-65.5)	0.130
ECMO-free days on day 28	0 (0-18.2)	10.1 (0-19.3)	0.075
Ventilator-free days on day 28	0 (0-0)	0 (0-8.5)	0.311
Ventilator-free days on day 60	0 (0-20.4)	8.3 (0-40.5)	0.04
Hospital mortality, n (%)	29 (70.7 %)	52 (46.8 %)	0.004

Data are presented as mean ± standard deviation, count or median (interquartile range)

ECMO extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *ICU* intensive care unit, *MP* mechanical power, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *PaO_2* partial pressure of oxygen in arterial blood, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *SOFA* Sequential Organ Failure Assessment

Table 3 Cox proportional hazard regression analysis of factors associated with 90-day hospital mortality

Variables	Univariate analysis		Multivariate analysis model 1		Multivariate analysis model 2		Multivariate analysis model 3	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (with each year increase)	1.018 (1.004-1.033)	0.012						
Pulmonary cause	1.989 (1.211-3.216)	0.007						
Extrapulmonary cause	0.785 (0.475-1.296)	0.344						
Diabetes mellitus	0.622 (0.358-1.079)	0.091						
Chronic liver disease	2.085 (1.184-3.670)	0.011						
Immunocompromised status	2.242 (1.411-3.563)	0.001	2.564 (1.488-4.419)	0.001	2.674 (1.556-4.596)	<0.001	2.554 (1.471-4.433)	0.001
ARDS duration before ECMO (with each hour increase)	1.002 (1.001-1.004)	<0.001	1.002 (1.001-1.004)	0.003	1.002 (1.001-1.004)	0.003	1.001 (1.000-1.003)	0.074
SOFA score from day 1 to 3 on ECMO (with each point increase)	1.318 (1.178-1.476)	<0.001	1.202 (1.067-1.355)	0.003	1.207 (1.074-1.356)	0.002	1.222 (1.084-1.377)	0.001
Tidal volume/PBW from day 1 to 3 on ECMO	1.001 (0.896-1.118)	0.992						
PEEP from day 1 to 3 on ECMO	0.945 (0.880-1.015)	0.120						
Peak inspiratory pressure from day 1 to 3 on ECMO	1.058 (1.019-1.100)	0.004						
Dynamic compliance from day 1 to 3 on ECMO	0.953 (0.924-0.984)	0.003						
Total respiratory rate from day 1 to 3 on ECMO	1.055 (1.003-1.109)	0.039						

MP from day 1 to 3 on ECMO	1.054 (1.017-1.093)	0.004	1.060 (1.018-1.104)	0.005				
MP/PBW from day 1 to 3 on ECMO (× 10^{-3}J/min/kg)	1.003 (1.001-1.005)	0.002			1.004 (1.002-1.007)	<0.001		
MP/compliance from day 1 to 3 on ECMO (J/min/ml/cm H_2O)	3.142 (1.966-5.020)	<0.001					2.289 (1.214-4.314)	0.010

ARDS acute respiratory distress syndrome, *CI* confidence interval, *ECMO* extracorporeal membrane oxygenation, *HR* hazard ratio, *MP* mechanical power, *PEEP* positive end-expiratory pressure, *PBW* predicted body weight, *SOFA* Sequential Organ Failure Assessment

Multivariate analysis models included age, pulmonary or extrapulmonary cause of ARDS, diabetes mellitus, chronic liver disease, immunocompromised status, ARDS duration before ECMO, SOFA score from day 1 to 3 on ECMO, ventilatory parameters from day 1 to 3 on ECMO (tidal volume/PBW, PEEP, peak inspiratory pressure, dynamic compliance, total respiratory rate)

Model 1: add MP from day 1 to 3 on ECMO

Model 2: add MP/PBW from day 1 to 3 on ECMO (× 10^{-3}J/min/kg)

Model 3: add MP/compliance from day 1 to 3 on ECMO (J/min/ml/cm H_2O)

Figures

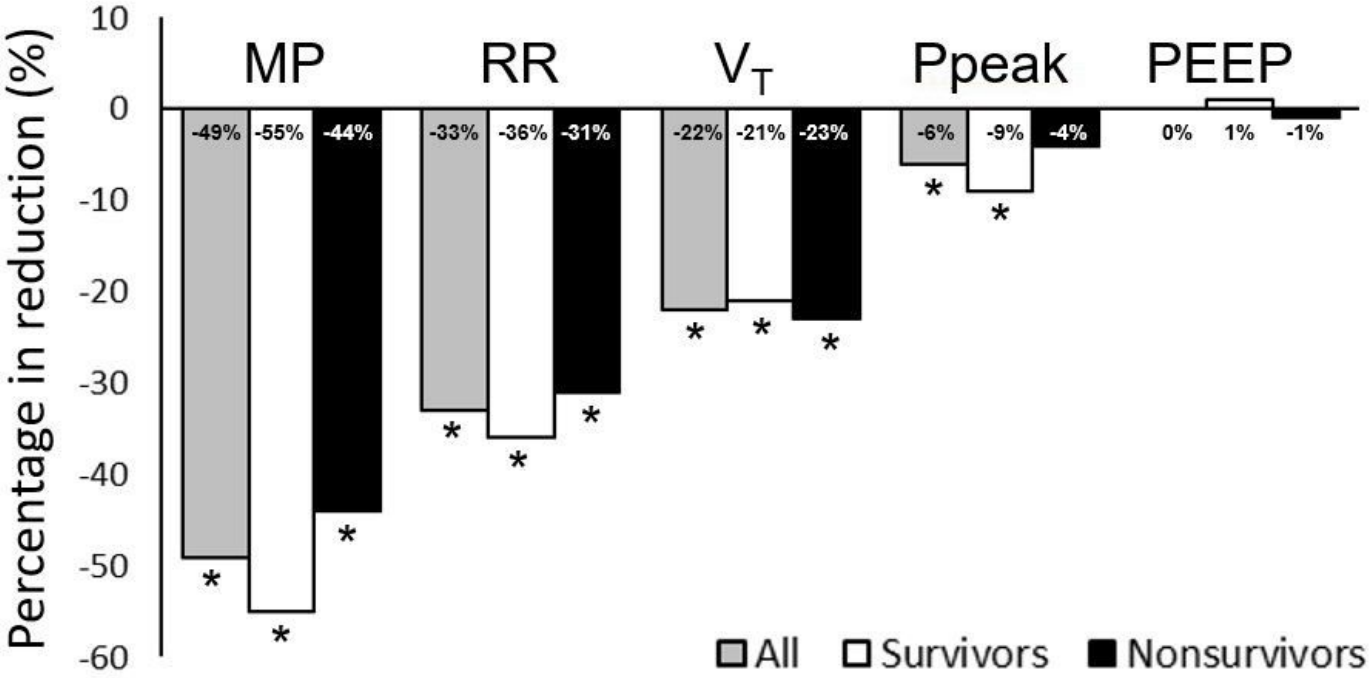
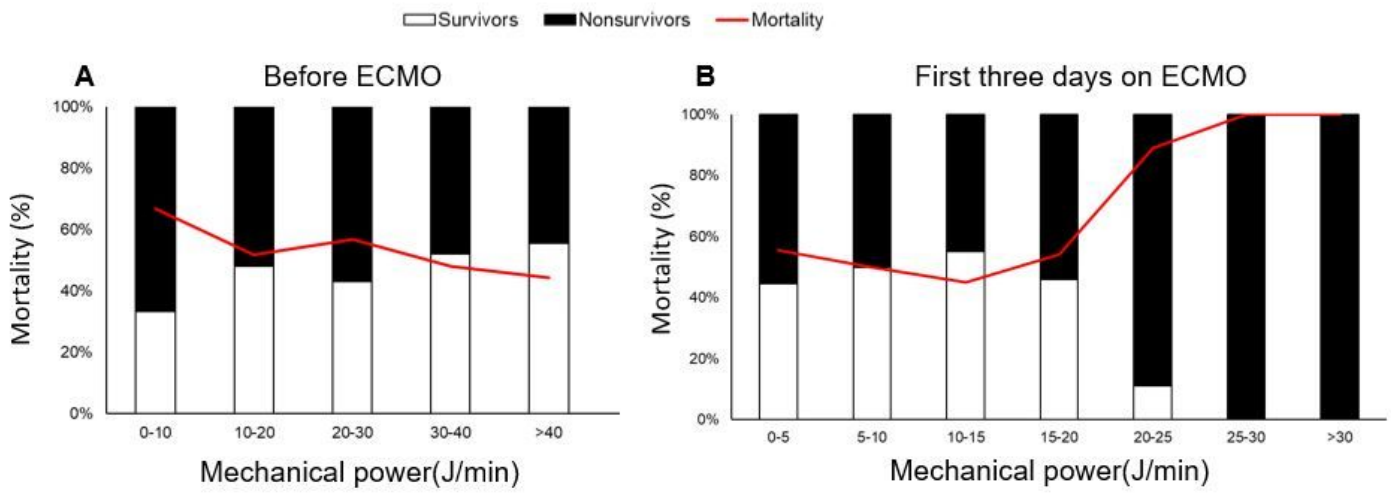


Figure 1

Difference in mechanical power and its determinants before extracorporeal membrane oxygenation (ECMO) and during the first 3 days of ECMO



Survivors	2	26	25	13	5	Survivors	4	28	27	11	1	0	0
Nonsurvivors	4	28	33	12	4	Nonsurvivors	5	28	22	13	8	3	2

Figure 2

a Hospital mortality as a function of MP before ECMO initiation. b During the first 3 days of ECMO. * p < 0.001 compared between the values before ECMO and during the first 3 days of ECMO. MP, mechanical power; RR, respiratory rate; VT , tidal volume; Ppeak, peak inspiratory pressure; PEEP, positive end-expiratory pressure

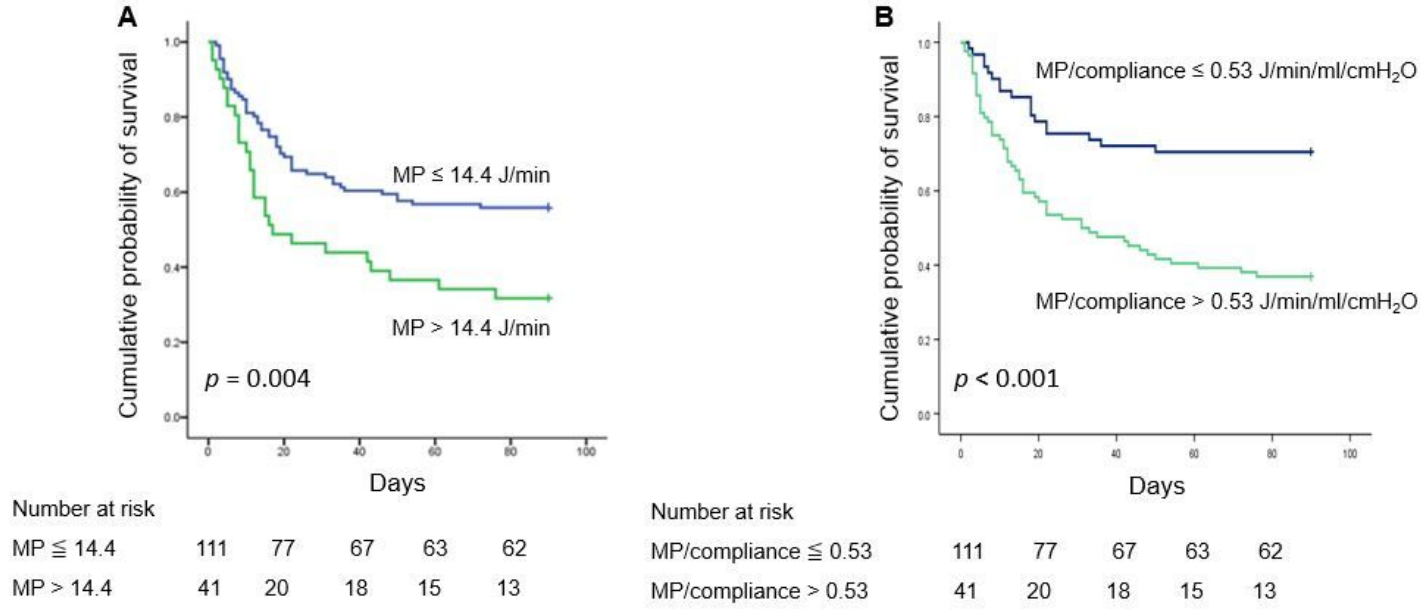


Figure 3

Kaplan-Meier 90-d survival curves of patients undergoing ECMO for severe acute respiratory distress syndrome, as stratified by the optimal cutoff value of a mechanical power (MP) (14.4 J/min). b MP normalized to compliance (0.53 J/min/ml/cm H2O)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx