Journal of Intensive Medicine 4 (2024) 194–201

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Original Article

Factors associated with decreased compliance after on-site extracorporeal membrane oxygenation cannulation for acute respiratory distress syndrome: A retrospective, observational cohort study

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ARTICLE INFO

Managing Editor: Jingling Bao/ Zhiyu Wang

Keywords:
Acute respiratory distress syndrome
Extracorporeal membrane oxygenation
Driving pressure
Respiratory compliance

ABSTRACT

Background: Extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) is systematically associated with decreased respiratory system compliance (CRS). It remains unclear whether transportation to the referral ECMO center, changes in ventilatory mode or settings to achieve ultra-protective ventilation, or the natural evolution of ARDS drives this change in respiratory mechanics. Herein, we assessed the precise moment when CRS decreases after ECMO cannulation and identified factors associated with decreased CRS.

Methods: To rule out the effect of transportation and the different modes of ventilation on CRS, we conducted a retrospective, single-center, observational cohort study from January 2013 to May 2020, on 22 patients with severe ARDS requiring on-site ECMO and ventilated in pressure-controlled mode to achieve ultra-protective ventilation. CRS was assessed at different time points ranging from 12 h before ECMO cannulation to 72 h after ECMO cannulation. The primary outcome was the relative change in CRS between 3 h before and 3 h after ECMO cannulation. The secondary outcomes included variables associated with the relative changes in CRS within the first 3 h after ECMO cannulation and the relative changes in CRS at each time point.

Results: CRS decreased within the first 3 h after ECMO cannulation (−28.3%, 95% confidence interval [CI]: −38.8 to −17.9, P<0.001), while the decrease was mild before and after these first 3 h after ECMO cannulation. To achieve ultra-protective ventilation, respiratory rate decreased in the mean by −13 breaths/min (95% CI: −15 to −11) and driving pressure by −8.3 cmH_2O (95% CI: −11.2 to −5.3), resulting in decreased tidal volume by −3.3 mL/kg of predicted body weight (95% CI: −3.9 to −2.6) as compared to before ECMO cannulation (P <0.001 for all). Plateau pressure reduction, driving pressure reduction, and tidal volume reduction were significantly associated with decreased CRS after ECMO cannulation, whereas neither respiratory rate, positive end-expiratory pressure, inspired fraction of oxygen, fluid balance, nor mean airway pressure was associated with decreased CRS.

Conclusions: Decreased driving pressure resulting in lower tidal volume to achieve ultra-protective ventilation after ECMO cannulation was associated with a marked decrease in CRS in ARDS patients with on-site ECMO cannulation.

Introduction

Veno-venous extracorporeal membrane oxygenation (ECMO) is a life-saving rescue therapy in patients with severe refractory acute respiratory distress syndrome (ARDS).[1–3] ECMO provides supplemental gas exchange [1] and may reduce ventilator-induced lung injury through the achievement of ultra-protective ventilation.[4,5] While usual protective ventilation settings target a tidal volume (VT) of 6 mL/kg and a plateau pressure (Pplat) <30 cmH_2O, experts recommend ultra-protective ventilation settings in patients treated with ECMO, targeting a positive end-expiratory pressure (PEEP) of at least 10 cmH_2O, in-

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https://doi.org/10.1016/j.jointm.2023.09.004
Received 5 July 2023; Received in revised form 11 September 2023; Accepted 26 September 2023
Available online 12 December 2023

spiratory Pplat <24 cmH_2O, driving pressure <14 cmH_2O targeting a VT <4 mL/kg of predicted body weight (PBW), and respiratory rate (RR) <10 cycles/minute.[6] In clinical practice, pressure-controlled ventilation modes are the most frequently used ventilation modes to achieve these goals.[7]

Dramatically decreased respiratory system compliance (CRS) is systematically reported after ECMO cannulation.[1,7,8] This decrease may be significant, as low CRS is independently associated with mortality in patients with ARDS whether treated with ECMO or not.[9,10] However, the cause of decreased CRS after ECMO cannulation has not yet been elucidated. In a retrospective cohort study, Rozé et al.[8] reported a 36% decrease in CRS 24 h after ECMO cannulation and ultra-protective pressure-controlled ventilation. As ECMO cannulation was performed outside the referral center, it cannot be verified whether the decreased CRS was because of transportation to the referral center or the worsening of lung injury in the course of ARDS. Another mechanism leading to the reduction of CRS could be alveolar derecruitment induced by ultra-protective ventilation. Several physiological studies showed that a reduction in VTs to achieve protective ventilation could induce alveolar derecruitment and progressively decreased compliance that could be prevented by the application of PEEP.[11–13]

We hypothesized that decreased CRS after ECMO cannulation for ARDS occurred in the very first hours after ECMO cannulation and was associated with changes in ventilatory settings to achieve ultra-protective ventilation. We aimed to assess changes in CRS after ECMO cannulation and the factors associated with decreased CRS.

Methods

Study design and patient selection

We conducted a single-center, retrospective, observational cohort study between January 2013 and May 2020 in the medical intensive care unit (ICU) of the University Hospital of Poitiers in France. The study was approved by the local ethics committee, and given its non-interventional nature, the need for informed consent was waived (CHU86-RECH-R2021–07–01).

All patients admitted to our referral ICU and required ECMO for severe ARDS according to the criteria defined in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) study were included.[1] To rule out the potential role of confounders such as transportation and ventilation mode, patients transported to our ICU after ECMO cannulation and those ventilated in volume-controlled mode after ECMO cannulation were excluded.

Management of patients

Before ECMO, patients were ventilated in volume-controlled mode according to recent clinical practice guidelines,[14] by using low VTs targeting 6 mL/kg of the PBW,[15] high PEEP targeting Pplat not exceeding 28–30 cmH_2O,[16] neuromuscular blockers when partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) remained <150 mmHg,[17] and 16-h sessions of prone positioning when PaO_2/FiO_2 remained <150 mmHg despite neuromuscular blockers.[18] Patients did not receive recruitment maneuvers.

ECMO was initiated when the PaO_2/FiO_2 was ≤80 mmHg for more than 6 h or <50 mmHg for more than 3 h, or when the pH was <7.25 with partial pressure of carbon dioxide ($PaCO_2$) ≥60 mmHg for more than 6 h.[1] All patients received sedatives and neuromuscular blockers during the first 72 h after ECMO cannulation and remained in a 30° reverse Trendelenburg position.

Immediately after ECMO cannulation, patients were ventilated in a pressure-controlled ventilation mode with the following settings: PEEP ≥10 cmH_2O, inspiratory pressure ≤25 cmH_2O, and inspiratory time adjusted to allow inspiratory flow to become nil so that inspiratory pressure equals Pplat and reflects end-inspiratory alveolar pressure.

Data collection

In addition to baseline characteristics at ICU admission, we collected the indication for ECMO cannulation according to the EOLIA criteria (i.e., PaO_2/FiO_2 <50 mmHg for more than 3 h, PaO_2/FiO_2 <80 mmHg for more than 6 h, or pH <7.25 with $PaCO_2$ ≥60 mmHg for more than 6 h);[1] the respiratory ECMO survival prediction score;[19] the rate of weaning from ECMO defined by the proportion of patients alive and weaned from ECMO; the durations of ECMO and mechanical ventilation; the length of ICU stay; and ICU mortality.

The following parameters were collected 12 h, 6 h, and 3 h before ECMO cannulation, and 3 h, 6 h, 12 h, 24 h, 48 h, and 72 h after ECMO cannulation: vital signs including heart rate, arterial blood pressure, RR, and pulse oximetry; arterial blood gasses; and ventilator settings including the FiO_2, RR, PEEP, Pplat, driving pressure (ΔP), mean airway pressure, and the resulting VT before and after ECMO. The ECMO settings including blood flow, sweep gas flow, and fraction of oxygen in the sweep gas were collected at each time point after ECMO cannulation.

Computations of respiratory mechanics

CRS was calculated as the VT divided by driving pressure. The driving pressure was calculated as Pplat minus PEEP. Relative changes in CRS between each time point were calculated as the difference in CRS between the two time points divided by the CRS at the earliest time point. Mean airway pressure and mechanical power were calculated as previously reported.[20,21]

Dead space fraction (VD/VT) was estimated using the unadjusted Harris-Benedict equation for the resting energy expenditure (REE) with the following formula:

$$\frac{VD}{VT} = 1 - \frac{0.863 \times VCO_2}{RR \times VT \times PaCO_2} \text{ with}$$

$$VCO_2 = \frac{REE}{\left(\frac{5.616}{RQ}\right) + 1.584} \text{ with}$$

REE (for males) = 66.473 + 13.752 × weight (kg) + 5.003 × height (cm) – 6.755 × age (years) or

REE (for females) = 655.096 + 9.563 × weight (kg) + 1.850 × height (cm) – 4.676 × age (years) and the respiratory quotient (RQ) = 0.8.[22]

$$\text{Ventilatory ratio} = \frac{\text{minute ventilation (mL/min)} \times \text{arterial } PCO_2 \text{ (mmHg)}}{\text{predicted body weight (kg)} \times 100 \times 37.5}.$$ [23]

To understand the effects of ventilatory setting changes to achieve ultra-protective ventilation on the changes in CRS, compliance of the "deventilated lung" was calculated as the VT reduction within the first 3 h after ECMO cannulation divided by the driving pressure reduction following ECMO cannulation, using the following formula:

$$\text{CRS of the deventilated lung} = \frac{VT_{H+3} - VT_{H-3}}{\Delta P_{H+3} - \Delta P_{H-3}}.$$

We assumed that this compliance of the "deventilated lung" would represent the compliance of the lung areas, which were not ventilated anymore using ultra-protective ventilatory settings.

Outcomes

The primary outcome was the relative changes in CRS between 3 h before and 3 h after ECMO cannulation to evaluate the proper effect of ECMO on respiratory mechanics between each time point. The secondary outcomes included: (1) variables associated with the relative changes in CRS within the first 3 h after ECMO cannulation, including changes in ventilator settings after ECMO cannulation (RR, driving pressure, Pplat, PEEP, and mean airway pressure), and variables known to influence CRS such as fluid balance as a surrogate of pulmonary edema,[24] and FiO_2 that can induce absorption atelectasis;[25] and (2) the relative changes in CRS at each time point (from 12 h before to 72 h after ECMO cannulation).

Statistical analysis

Qualitative variables were expressed as numbers and percentages. Continuous variables were expressed as mean±standard deviation or median (interquartile range). For each continuous variable, mean differences between 3 h before and 3 h after ECMO cannulation and their 95% confidence intervals (CIs) were calculated and compared using the paired *t*-test.

To assess the relationship between variables and the relative change in CRS between 3 h before and 3 h after ECMO cannulation, Pearson's rho correlation coefficient (95% CI) and simple linear regression were calculated. Two-tailed P <0.05 was considered significant. Statistical analyses were conducted with R software version 3.6.1, available at https://www.r-project.org.

Results

Over the study period, 48 patients with ECMO for severe ARDS were treated in our unit. After excluding 17 patients who were transferred to our unit after ECMO cannulation and 9 patients who were ventilated in volume-controlled mode after ECMO cannulation, 22 patients were retained in the analysis. Characteristics of the patients are displayed in Table 1. ECMO was weaned in 15 out of 22 patients (68.2%), and 13 out of 22 patients (59.1%) were discharged alive from the ICU. The initial ECMO settings were as follows: mean ECMO blood flow was (4.3±0.9) L/min; mean fraction of oxygen in the sweep gas was 0.88±0.16; and mean sweep gas flow was (4.7±1.3) L/min.

Table 1
Baseline characteristics and outcomes (n = 22).

Variables	Data
Demographic characteristics	
Age (years)	53 ± 15
Sex male	14 (63.6)
Body-mass index (kg/m^2)	30 ± 7
Immunocompromised status	3 (13.6)
Characteristics at ICU admission	
Simplified Acute Physiology score 2	46 ± 19
Sequential Organ Failure Assessment score	9 ± 5
Reason for ICU admission	
Acute respiratory failure	20 (90.90)
Shock	1 (4.55)
Cardiac arrest	1 (4.55)
Pulmonary ARDS	18 (81.8)
Viral pneumonia	12/18 (54.5)
Bacterial pneumonia	4/18 (18.1)
Other*	2/18 (9.0)
Time from ICU admission to intubation (days)	1 (1–2)
Treatments prior to ECMO cannulation	
Neuromuscular blockers	22 (100)
Prone positioning	20 (90.9)
Steroids	1 (4.5)
Nitric oxide	4 (18.2)
Norepinephrine	16 (72.7)
Renal replacement therapy	1 (4.5)
Characteristics related to ECMO	
RESP score	2.4 ± 2.3
Risk class I	2 (9.0)
Risk class II	10 (45.5)
Risk class III	9 (40.9)
Risk class IV	1 (4.5)
Risk class V	0 (0)
Time from intubation to ECMO cannulation (days)	4 (1–6)
Indication for ECMO cannulation	
PaO_2/FiO_2 <80 mmHg for >6 h	18 (81.8)
PaO_2/FiO_2 <50 mmHg for >3 h	2 (9.0)
pH <7.25 with $PaCO_2$ ≥60 mmHg for >6 h	2 (9.0)
Outcomes	
Weaning from ECMO	15 (68.2)
ECMO duration (days)	12 (7–17)
Mechanical ventilation duration (days)	20 (16–32)
ICU stay (days)	29 (17–34)
ICU mortality	9 (40.9)

Data are expressed as n (%), mean±standard deviation, or median (interquartile range).

* Other pulmonary ARDS etiologies included one pulmonary lymphoma and one toxic pneumonitis.

ARDS: Acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; ICU: Intensive care unit; PaO_2/FiO_2: Partial pressure of oxygen /fraction of inspired oxygen; RESP: Respiratory extracorporeal membrane oxygenation survival prediction.

Changes in ventilatory settings

Changes in ventilatory settings at the time of ECMO cannulation to achieve ultra-protective ventilation are displayed in Table 2.

The Pplat decreased from (30.2±4.7) cmH_2O to (25.0±2.0) cmH_2O (mean reduction of −5.2 cmH_2O ,95% CI: −7.4 to −3.0; P <0.001) and PEEP increased from (10.6±4.4) cmH_2O to (13.7±2.0) cmH_2O (mean increase of 3.1 cmH_2O, 95% CI: 0.9–5.3; P=0.009), resulting in the decrease of the driving pressure, which decreased from (19.6±6.8) cmH_2O to (11.3±2.3) cmH_2O (mean reduction of −8.3 cmH_2O, 95% CI: −11.2 to −5.3; P <0.001) (Figure 1A). As a result, VT decreased from (6.3±0.9) mL/kg of PBW to (3.0±1.5) mL/kg of PBW (mean reduction of −3.3 mL/kg of PBW, 95% CI: −3.9 to −2.6; P <0.001). Likewise, RR decreased from (32 ± 3) breaths/min to (19 ± 5)

Table 2
Ventilatory characteristics with respect to ECMO cannulation.

Items	3 h before ECMO cannulation	3 h after ECMO cannulation	Mean difference (95% CI)	*P*-value
FiO_2 (%)	98±6	70±19	−28 (−36 to −20)	<0.001
Tidal volume (mL/kg of PBW)	6.3±0.9	3.0±1.5	−3.3 (−3.9 to −2.6)	<0.001
PEEP (cmH_2O)	10.6±4.4	13.7±2.0	3.1 (0.9 to 5.3)	0.009
Plateau pressure (cmH_2O)	30.2±4.7	25.0±2.0	−5.2 (−7.4 to −3.0)	<0.001
Driving pressure (cmH_2O)	19.6±6.8	11.3±2.3	−8.3 (−11.2 to −5.3)	<0.001
CRS (mL/cmH_2O)	21.1±8.7	15.7±8.4	−5.4 (−7.4 to −3.5)	<0.001
Mean airway pressure (cmH_2O)	19.0±3.2	17.2±2.4	−1.8 (−3.7 to 0.2)	0.076
RR (cycles/min)	32±3	19±5	−13 (−15 to −11)	<0.001
Minute ventilation (L/min)	11.4±2.4	3.2±1.9	−8.2 (−9.2 to −6.8)	<0.001
Mechanical power (J/min)	41.9±12.4	7.5±4.8	−34.4 (−39.7 to −29.0)	<0.001
Ventilatory ratio	3.4±0.9	NA	NA	NA
Dead space fraction	0.77±0.07	NA	NA	NA
PaO_2/FiO_2 (mmHg)	66±15	NA	NA	NA
PaO_2 (mmHg)	65±15	92±66	27 (−2 to 56)	0.064
pH	7.23±0.11	7.38±0.10	0.15 (0.11 to 0.19)	<0.001
$PaCO_2$ (mmHg)	66±19	41±9	−25 (−32 to −18)	<0.001
Bicarbonate (mmol/L)	27.0±8.9	24.1±8.0	−2.9 (−3.9 to −1.9)	<0.001
Lactate (mmol/L)	2.03±1.14	2.61±1.78	0.54 (0.11 to 0.97)	0.016
Norepinephrine ($\mu g/kg/min$)	0.69±1.05	0.74±1.20	0.11 (−0.29 to 0.51)	0.563
Mean arterial pressure (mmHg)	80±12	81±12	1 (−4 to 6)	0.703
Heart rate (beats/min)	115±20	98±22	−20 (−29 to −10)	<0.001
Fluid balance (mL/kg) of body weight	22.4±30.9	47.2±43.3	30.4 (21.4 to 39.3)	<0.001

Data are expressed as mean±standard deviation.
CI: Confidence interval; CRS: Respiratory system compliance; ECMO: Extracorporeal membrane oxygenation; FiO_2: Inspired fraction of oxygen; NA: Not available; $PaCO_2$: Partial pressure of arterial carbon dioxide; PaO_2: Partial pressure of arterial oxygen; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; RR: Respiratory rate.

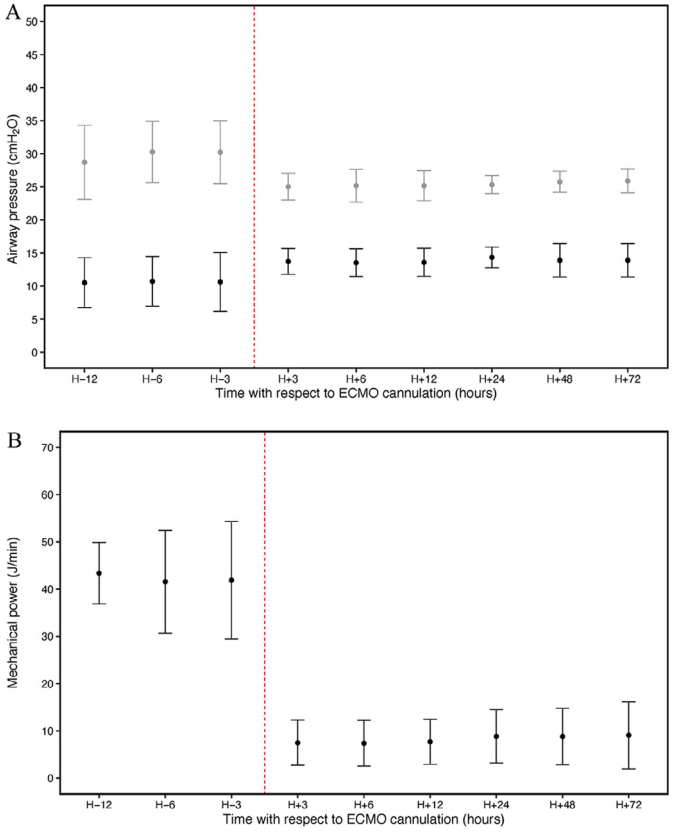

Figure 1. Changes in airway pressures and mechanical power over time. A: Evolution of end-expiratory pressure (black) and end-inspiratory pressure (gray) settings at each time point. B: Evolution of mechanical power at each time point. The vertical red dotted line represents the time of ECMO cannulation. The mean value of each time point is represented with error bars representing the standard deviation.
ECMO: Extracorporeal membrane oxygenation.

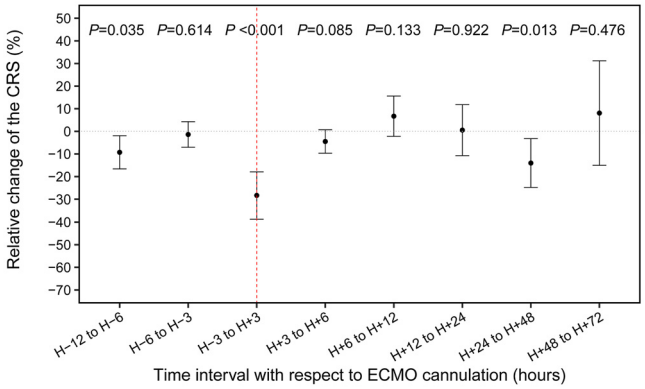

Figure 2. Relative changes of CRS over time. The mean relative change in CRS between each time point is represented with its 95% CI, starting from 12 h before ECMO cannulation to 72 h after ECMO cannulation. *P*-values measure the statistical difference between two consecutive time intervals. The vertical red dotted line represents the time of ECMO cannulation.
CI: Confidence interval; CRS: Respiratory system compliance; ECMO: Extracorporeal membrane oxygenation.

breaths/min (mean reduction of –13 breaths/min, 95% CI: –15 to – 11; *P* <0.001), resulting in decreased mechanical power from (41.9±12.4) J/min to (7.5±4.8) J/min (mean reduction of −34.4 J/min, 95% CI: −39.7 to −29.0; *P* <0.001) (Figure 1B).

Changes in CRS over time

CRS decreased over time, from (25.1±10.3) mL/cmH_2O 12 h before ECMO cannulation to (13.1±8.2) mL/cmH_2O 72 h after ECMO cannulation (Supplementary Table S1 and Supplementary Figure S1). The most important decrease in CRS occurred between 3 h before and 3 h after ECMO cannulation (from (21.1±8.7) mL/cmH_2O to (15.7±8.4) mL/cmH_2O), rep-

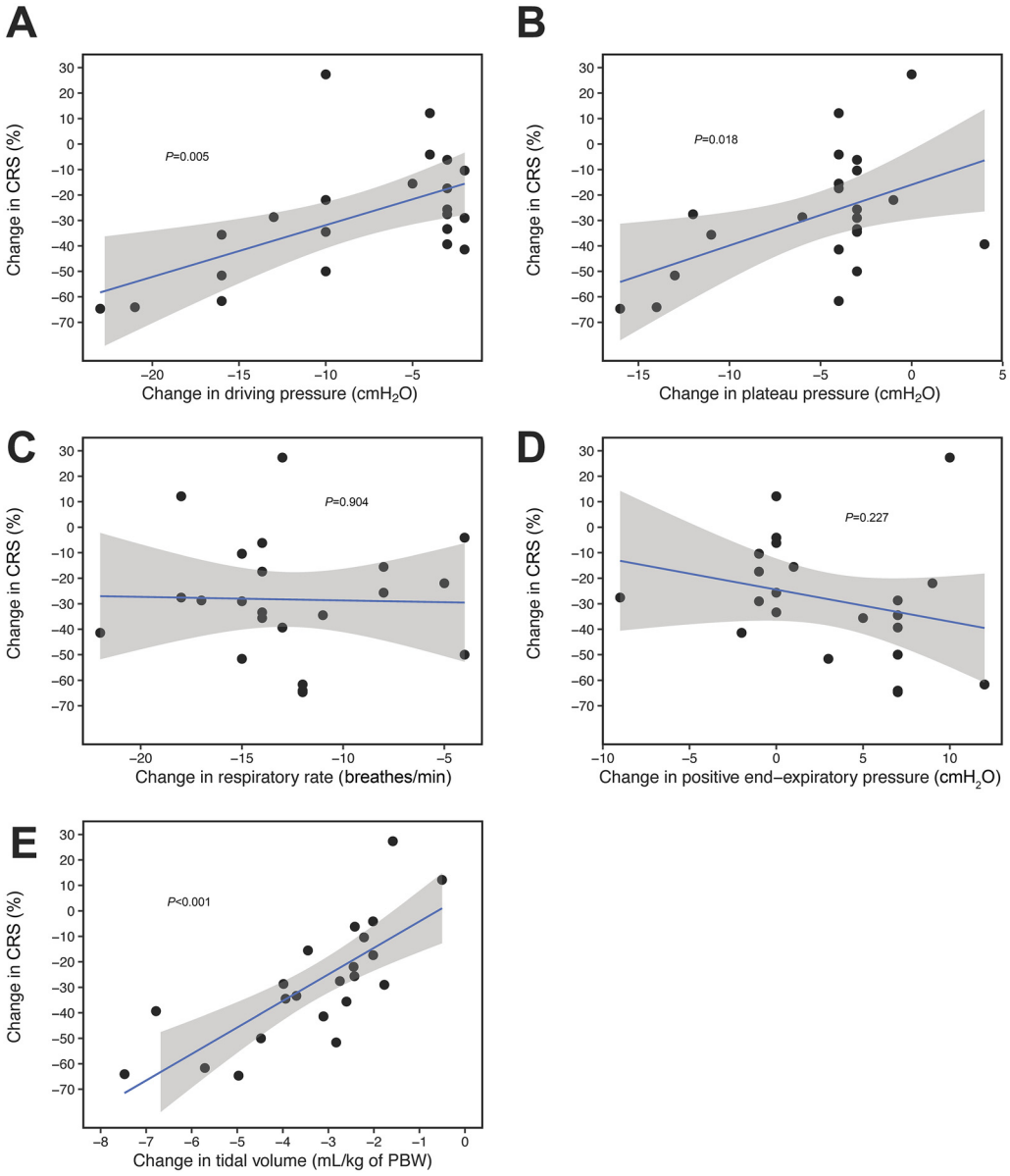

Figure 3. Correlation between changes of CRS between 3 h before and 3 h after ECMO cannulation and the corresponding changes in ventilator settings. A: Driving pressure. B: Plateau pressure. C: Respiratory rate. D: Positive end-expiratory pressure. E: Corresponding changes of tidal volume per PBW.
CRS: Respiratory system compliance; ECMO: Extracorporeal membrane oxygenation; PBW: Predicted body weigh.

resenting a relative decrease in CRS by −28.3% (95% CI: −38.8 to −17.9, P <0.001, Figure 2).

Factors associated with CRS decrease within the first 3 h after ECMO cannulation

Decreased CRS within the first 3 h after ECMO cannulation was significantly correlated with driving pressure reduction (r=0.57, 95% CI: 0.20–0.80, P=0.005), Pplat reduction (r=0.50, 95% CI: 0.10–0.76, P=0.018), and VT reduction (r=0.76, 95% CI: 0.49–0.89, P <0.001). By contrast, PEEP increase, RR decrease, FiO_2 changes, mean airway pressure changes, and fluid balance were not associated with decreased CRS within the first 3 h after ECMO cannulation (Figure 3).

Interestingly, compliance of the deventilated lung after ECMO cannulation was higher than the overall CRS before ECMO cannulation: (35.4±24.2) mL/cmH_2O *vs.* (21.1±8.7) mL/cmH_2O (P <0.001), suggesting deventilation of lung areas with relatively high compliance. Compliance of the deventilated lung was higher than 40 mL/cmH_2O in 8 out of 22 patients (36.4%) (Figure 4).

Discussion

In this cohort of severe ARDS patients treated on-site with ECMO, changes in ventilatory settings to achieve ultra-protective ventilation under ECMO were associated with significantly decreased CRS by 28.3% within the first 3 h following ECMO cannulation, whereas CRS decreased only mildly be-

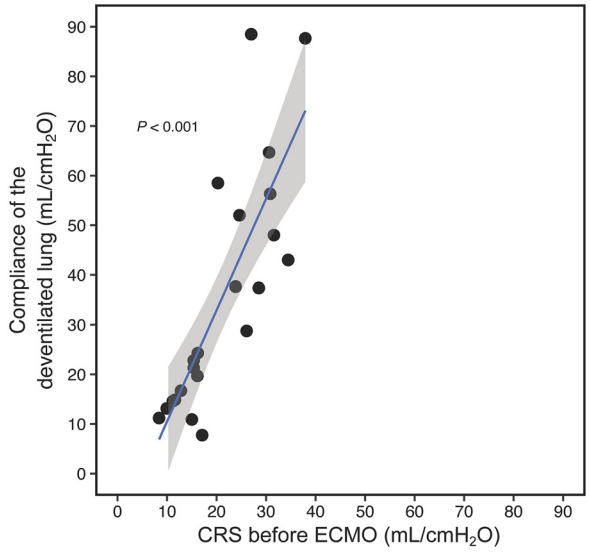

Figure 4. Compliance of the deventilated lung according to CRS before ECMO cannulation.
CRS: Respiratory system compliance; ECMO: Extracorporeal membrane oxygenation.

fore or late after ECMO cannulation. Driving pressure reduction, Pplat reduction, and VT reduction were significantly correlated with this CRS decrease, suggesting that the greater the reduction in driving pressure, Pplat, and VT, the greater the decrease in CRS. Additionally, compliance of the deventilated lung after ECMO cannulation was significantly higher than CRS before ECMO cannulation. As patients transported after ECMO cannulation and patients ventilated in volume-controlled ventilation mode were excluded, our data suggest that changes to the ventilatory settings to achieve ultra-protective ventilation after ECMO cannulation were associated with CRS decrease through the deventilation of relatively compliant lung regions.

Decreased CRS 24 h after ECMO cannulation has been systematically reported in observational cohorts and randomized trials.[1,7,8] It was hypothesized that this decreased CRS could be because of transportation after ECMO cannulation, of the natural evolution of the disease, or of changes in ventilatory settings. However, the proportion of patients transported after ECMO and ventilatory settings was highly variable from one study to another, making it difficult to differentiate the respective effects of transportation from that of changes in ventilator settings on decreased CRS. In one trial, 55% of patients were transported after ECMO cannulation, and all patients were ventilated in pressure-controlled mode;[1] whereas, in a large-scale international cohort, 40% of patients were transported after ECMO cannulation and 69% of patients were ventilated in pressure-controlled mode.[7] Moreover, assessment of changes in CRS 24 h after ECMO cannulation may be too late to differentiate the influence of the changes in ventilator settings from the consequences of the natural evolution of ARDS or transportation. Of note, while transportation has been associated with oxygen desaturation,[26] it has never been associated with alveolar derecruitment. According to our longitudinal measurements ranging from 12 h before to 72 h after ECMO cannulation, the most important CRS decrease occurred within the first 3 h after ECMO cannulation, suggesting an association with changes in ventilatory settings rather than with the natural evolution of ARDS.

Several factors have been associated with changes in CRS in the literature. An experimental study suggested that changes in CRS could be because of changes in mean airway pressure.[27] However, mean airway pressure did not significantly decrease after cannulation in our study. While Pplat markedly decreased after ECMO cannulation, PEEP was significantly increased to maintain a stable mean airway pressure. High FiO_2 could also decrease CRS through denitrogenation atelectasis.[25] Although FiO_2 was significantly lower after than before ECMO cannulation, we cannot rule out this mechanism given the imbalance between the high fraction of oxygen delivered by the ECMO and decreased FiO_2 after ECMO cannulation. Last, at ECMO cannulation, we observed increased lactate level and weight-adjusted fluid balance – the latter resulting partly from the ECMO circuit priming – but the norepinephrine level and the mean arterial pressure were unchanged. Although hydrostatic pulmonary edema may alter CRS,[28] increased weight-adjusted fluid balance after ECMO cannulation was not significantly correlated with decreased CRS. Hence, the hemodynamic variations do not account for the decreased CRS. Increased PEEP is associated with decreased CRS in patients independently from the potential for lung recruitment through lung overdistension.[29] In our study, PEEP increased dramatically within the first 3 h after ECMO cannulation. However, Pplat was reduced, hence ruling out overdistension at end-inspiration. Moreover, increased PEEP after ECMO cannulation could have blunted the natural decrease in CRS. Additionally, there was no correlation between increased PEEP and decreased CRS. The only ventilatory settings associated with decreased CRS after ECMO cannulation were Pplat reduction, driving pressure reduction, and the subsequent VT reduction. Importantly, prone positioning patients under ECMO can increase CRS.[30] Most of our patients underwent at least one prone position session before ECMO cannulation, whereas they remained in the reverse Trendelenburg position within the first 72 h after ECMO cannulation. Therefore, we cannot rule out that stopping prone positioning after ECMO cannulation could have contributed to decreased CRS.

Several physiological studies in volume-controlled ventilation have shown that the reduction of VTs and of the resulting driving pressure induces significant alveolar derecruitment and decreased CRS.[11–13] However, these studies also showed that alveolar derecruitment induced by the reduction of VTs could be limited by increasing PEEP. In our study, although the PEEP level was significantly increased after ECMO cannulation, driving pressure reduction induced a dramatic decrease in CRS, suggesting dramatic alveolar derecruitment. A possible explanation could be the difference in the VTs reached. However, in physiological studies, VTs were reduced from conventional (around 10 mL/kg of PBW) to protective (around 6 mL/kg of PBW), and our changes in ventilatory settings reduced VTs from protective to ultra-protective ventilation (around 3 mL/kg of PBW). Such VT reduction may lead to marked alveolar derecruitment despite increased PEEP. Even though ultra-protective ventilation lowering VTs to 3 mL/kg of PBW may be associated with lower lung inflammation,[31] potential survival benefits have not yet been demonstrated,[32] and further VT reduction on outcomes is conflicting.[33–35]

Interestingly, compliance of the "deventilated lung" after ECMO cannulation, i.e., the change in VT divided by the change in driving pressure to achieve ultra-protective ventilation was relatively high as compared to CRS before ECMO cannulation. It could be hypothesized that low PEEP and high driving pressure before ECMO cannulation were associated with high tidal recruitment (reopening during insufflation of lung areas that close during expiration), and that increased PEEP with decreased driving pressure after ECMO cannulation would reduce this phenomenon.[36] Decreased tidal recruitment after the change of ventilatory settings to achieve ultra-protective ventilation might explain the relatively high compliance of the "deventilated lung" after ECMO cannulation, and the decreased CRS we observed within the first 3 h after ECMO cannulation. This hypothesis merits confirmation. It remains to be determined whether ultra-protective ventilation is deleterious by decreasing CRS, which is associated with increased mortality [37] or beneficial by mitigating ventilation-induced lung injury.

Limitations

Our study has some limitations. First, the retrospective nature of our study could have led to selection bias. However, the characteristics of our patients were similar to those found in large-scale studies on ECMO during ARDS, reinforcing the external validity of our results.[1,7] Second, the study sample size was small; hence, the impact of decreased CRS on outcomes could not be adequately tested. Our results need to be confirmed in a larger cohort. Third, PEEP was significantly higher after than before ECMO cannulation in our cohort and may have led to overdistension of the aerated lung. Although higher than in large studies,[1,7] our PEEP settings were in line with those proposed by international experts.[6] Fourth, we did not partition the respiratory system mechanics to support our hypothesis that changes in ventilator settings lead to alveolar derecruitment. However, it is very unlikely that decreased chest wall compliance after ECMO cannulation could be sudden and explain the decreased CRS. Fifth, the observed decreased CRS 24 h after ECMO cannulation was very close to that reported in the EOLIA trial. The main difference with the EOLIA trial is the compliance before ECMO cannulation, which was lower in our cohort than in EOLIA. This difference can be explained by the longer time from intubation to ECMO cannulation in our cohort than in EOLIA (4 days [1–6] *vs.* 1 day [1–4]) and thus a longer exposition to ventilator-induced lung injury.

Conclusions

In this retrospective cohort study of patients with severe ARDS ventilated in pressure-controlled mode and treated with on-site ECMO, CRS decreased by 28.3% within the first hours after ECMO cannulation. Decreased CRS was associated with changes in ventilator settings to achieve ultra-protective ventilation; specifically, Pplat and driving pressure reduction may lead to deventilation of a relatively compliant lung. Further research is needed to better understand the risks and benefits of ultra-protective ventilation during ECMO.

Author Contributions

Rémi Coudroy and **Arnaud W. Thille** contributed to the conception and design of the study. **Sylvain Le Pape** and **Florent Joly** collected patients' data. **Sylvain Le Pape** and **Rémi Coudroy** performed the statistical analysis. **Sylvain Le Pape, Florent Joly, François Arrivé, Jean-Pierre Frat, Maeva Rodriguez, Maïa Joos, Laura Marchasson, Mathilde Wairy, Arnaud W. Thille**, and **Rémi Coudroy** made substantial contributions to the original drafting and revising of the manuscript. **Arnaud W. Thille** and **Rémi Coudroy** provided daily assistance and professional comments on the manuscript. **Rémi Coudroy** is responsible for the overall content as guarantor. All authors read and approved the final manuscript for publication.

Acknowledgments

We gratefully thank Jeffrey Arsham for reviewing and editing the original English-language manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Statement

The study was approved by the local ethics committee, and given its non-interventional nature, the need for informed consent was waived (CHU86-RECH-R2021-07-01). Some of the results had previously been reported in abstract form at the annual meeting of the French Intensive Care Society (June 9–11, 2021) in Paris, France.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data are available from the corresponding author on reasonable request.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jointm.2023.09.004.

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