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Association of Respiratory Parameters at Venovenous Extracorporeal Membrane Oxygenation Liberation With Duration of Mechanical Ventilation and ICU Length of Stay: A Prospective Cohort Study

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OBJECTIVES: Although the criteria for initiation of venovenous extracorporeal membrane oxygenation (VV ECMO) are well defined, the criteria and timing for VV ECMO decannulation are less certain. The aim of this study was to describe the ventilation and physiologic factors at the time of VV ECMO decannulation and to determine if these factors have association with mechanical ventilation or ICU length of stay after ECMO decannulation.

DESIGN: Multicenter, prospective cohort study.

SETTING: Eleven ICUs in Australia.

PATIENTS: Adult patients treated with VV ECMO from March 19, 2019, to September 20, 2020.

INTERVENTIONS: Liberation from VV ECMO.

RESULTS: Of 87 patients receiving VV ECMO, the median age was 49 years (interquartile range, 37–59 yr), 61 of 87 (70%) were male, and 52/87 (60%) had a diagnosis of acute respiratory distress syndrome. There were 24 of 87 patients (28%) who died prior to day 90. No patient required a second run of VV ECMO. In a multivariate models, a higher partial pressure of arterial carbon dioxide ($p < 0.01$) and respiratory rate at the time of decannulation ($p = 0.01$) were predictive of a longer duration of mechanical ventilation and ICU length of stay post-decannulation in survivors. Higher positive end-expiratory pressure at ECMO decannulation was associated with shorter duration of ICU length of stay post-ECMO decannulation in survivors ($p = 0.01$).

CONCLUSIONS: A higher partial pressure of arterial carbon dioxide and higher respiratory rate at ECMO decannulation were associated with increased duration of mechanical ventilation and increased duration of ICU stay postdecannulation, and increased positive end-expiratory pressure at decannulation was associated with decreased duration of ICU stay postdecannulation. Future research should further investigate these associations to establish the optimal ventilator settings and timing of liberation from VV ECMO.

KEY WORDS: acute respiratory distress syndrome; extracorporeal membrane oxygenation; venovenous; weaning

Venovenous extracorporeal membrane oxygenation (VV ECMO) has been shown to improve mortality (1) for patients with severe acute respiratory distress syndrome (ARDS), and its use is increasing globally (2). VV ECMO provides rescue therapy for severe hypoxia and hypercapnia, but it may also confer benefit by facilitating lung-protective ventilation

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strategies and preventing ventilator-induced lung injury (VILI) (3, 4). Although the indications for starting VV ECMO therapy have been extensively studied and are supported by international guidelines (2, 3), evidence regarding the optimal timing of decannulation from VV ECMO (also known as "liberation") is limited.

Decannulation from VV ECMO occurs once clinicians decide that the underlying pathology has improved, and patients can be safely transitioned from membrane to native lung. Weaning from VV ECMO is relatively simple, as clinicians can simply turn off the fresh gas flow (FGF), while maintaining blood flow through the ECMO circuit. This is followed by a period of observation to see how well the patient tolerates being off ECMO support (4). Usually, if the patient does not develop instability or worsening mechanical ventilation (MV) parameters, the patient can be decannulated. However, due to the complex interplay between the mechanical ventilator and ECMO circuit, it is possible to decannulate a patient from ECMO earlier or later in the course of their illness depending on the amount of support provided by the mechanical ventilator. Historically, there has been little data to guide clinicians about the optimal timing of ECMO decannulation or the impact that different ventilator settings have on patient outcomes, and practice is based on institutional and expert opinion (5–8). Recently, Al-Fares et al (9) and Gannon et al (10) have provided patient data regarding prediction of safe liberation and protocolized assessments for liberation. The aim of this study was to describe the ventilation and physiologic factors at the time of VV ECMO decannulation and to determine if these factors impact duration of MV or ICU length of stay (LOS) after VV ECMO decannulation.

MATERIALS AND METHODS

Study Design, Setting, and Population

This was a multicenter, prospective cohort study using a national ECMO database (EXCEL NCT03793257) across Australia. Ethical approval was obtained prior to commencing the study (The Alfred HREC 534/18), including a waiver of consent for hospital data. Patients were treated at 11 ICUs in Australia that have expertise in managing VV ECMO by Intensive Care Specialists. All patients that received VV ECMO from March 19, 2019, to September 20, 2020, were included in the study. We excluded any patients that received venoarterial (VA) ECMO at any point during this period.

ECMO Management

The criteria for initiation of VV ECMO were severe hypoxia refractory to conventional therapies and/or hypercarbia while trying to maintain protective lung ventilation parameters (3, 11). Intensive Care Specialists with training in cannulation used a percutaneous Seldinger technique guided by ultrasound (12, 13). Patients who were at a non-ECMO-capable center were initiated on ECMO and had an interhospital transfer to an ECMO-capable hospital, the details of which have been previously described (14). Weaning from VV ECMO and decannulation is largely governed by hospital guidelines and expert opinion. Per local guideline and practice, the patients were assessed daily for improvements in respiratory function and overall clinical condition. This included tolerating a low ECMO blood flow less than 2.5 L/min, safe lung ventilation with low levels of ventilatory support, the absence of increase work of breathing on low FGF settings, and radiological clearance of the initial pathology on chest radiograph; the criteria of safe lung ventilation and increased work of breathing were not defined or protocolized a priori across sites. Once the patients met these criteria, the FGF (set at 100% O_2 previously) on the ECMO circuit was turned off and observed for a period of 4–24 hours, followed by decannulation.

Data Management and Collection

Data were prospectively collected by ICU research coordinators at each ICU for demographics, severity of illness, and physiologic parameters on the day of admission to ICU and on the day prior to VV ECMO commencement. Data were collected for severity of illness, physiologic parameters, VV ECMO cannulation details, ECMO settings, and adverse events on the day VV ECMO was initiated and for the following 7 days and again on the day of decannulation with worst values being collected. The outcomes measured included total duration of VV ECMO, requirements for decannulation or reconfiguration of VV ECMO, total duration of MV, days in ICU after decannulation, and 90-day mortality.

Statistical Analysis

Patient characteristics at baseline were reported as percentages for categorical variables and as means (with standard deviations) or medians (with interquartile ranges [IQRs]) for continuous variables, as appropriate. Missing data were assumed to be missing at random given all parameters were collected in the ICU; complete case analysis was used for outcome and predictor with simple single imputation for continuous covariates (**E-Table 2**, http://links.lww.com/CCX/A982). Categorical outcomes were assessed with logistic regression with reported odds ratios. In survivors, continuous outcomes were compared with multivariable linear regression to control for confounding using the physiologic and laboratory variables available during decannulation in examining for a relationship with duration of MV and ICU LOS: continuous renal replacement therapy (CRRT) use, $Paco_2$, Pao_2 to Fio_2 ratio (P:F), peak pressure (PP), tidal volume (TV) in mL/kg using predicted body weight, respiratory rate (RR) and positive end-expiratory pressure (PEEP), total duration of ECMO, duration of MV prior to decannulation, body mass index (BMI), pH, and age. Models were tested for linearity, and R^2 value for duration of MV and length of ICU stay postdecannulation were 54% and 51%, respectively. These confounders were determined a priori based on clinical relevance. These variables were collected once per day for first 7 days and immediately prior to decannulation. Univariate analysis with decannulation median values of PEEP, $Paco_2$, and RR was compared with study outcomes of ICU LOS and duration of MV. PEEP values at decannulation in increments of 5 cm H_2O were assessed for differences in ICU LOS. All analyses were conducted with a two-sided alpha level of 5% and were performed in the STATA software, Version 16.1 (StataCorp LLC, College Station, TX, 2019).

Outcomes

The primary outcome was duration of MV and length of ICU stay postdecannulation. Secondary clinical outcomes included the number of patients that were liberated from ECMO, the rate of recannulation of ECMO, and overall survival to 90 days.

RESULTS

From March 19, 2019, to September 20, 2020, 87 patients required VV ECMO at 11 sites across Australia. Patients commencing ECMO had a median age of 49 years (IQR, 37–59 yr), and 61 of 87 (70%) were male (**Table 1**). Of the patients, 83 of 87 (96%) were cannulated for hypoxemic respiratory failure, and 52 of 87 (60%) had a diagnosis of ARDS (etiology reflected in Table 1). Prior to ECMO, 10 of 87 patients (11%) received prone ventilation, and 37 of 87 patients (43%) received neuromuscular blockade. The median duration of MV prior to ECMO was 14.9 hours (IQR, 6.3–121.2 hr). The median duration of ECMO and MV was 9 days (IQR, 5–16 d) and 16 days (IQR, 9–28 d), respectively. Mortality at 30 and 90 days was 21 of 87 (24%) and 24 of 87 (28%) (**Table 2**). No patients require a second initiation of ECMO due to a failed decannulation attempt. Patient's pre-VV ECMO Pao_2:Fio_2, $Paco_2$, and MV duration were not predictive of mortality (**E-Table 1**, http://links.lww.com/CCX/A982).

At the time of decannulation, patients had a median P:F of 217 (IQR, 173–300), median $Paco_2$ of 46 mm HG (IQR, 38–48), median PEEP of 10 cm H_2O (IQR, 7.5–12), median RR of 20 breaths/min (IQR, 15–22), and median dynamic compliance of 31 mL/cm H_2O (IQR, 21–40) (**Table 3**). After ECMO decannulation, patients had a median duration of 7 days (3-15) on MV and 11 days (IQR, 5–23 d) in ICU (**Table 4**).

Using a multivariable model in survivors (adjusting for CRRT use, arterial carbon dioxide, P:F, PP, TV in mL/kg using predicted body weight, RR, PEEP, total duration of ECMO, duration of MV prior to decannulation, BMI, pH, and age), we found for a 1 mm Hg increase in $Paco_2$, there was a 0.80-day increase in duration of MV post-decannulation (p value < 0.01) and a 0.87-day increase in ICU LOS postdecannulation (p value < 0.01) (Table 4). For RR, the adjusted analysis showed a 1.26-day (p value = 0.01) increase in MV postdecannulation and a 1.14-day (p value < 0.01) increase in ICU LOS for every 1 increase in breath/min. We found that a 1-cm H_2O increase in PEEP was associated with a decrease of 1.84 days in ICU LOS postdecannulation in the adjusted regression model (Table 4).

Patients were also dichotomized based on median $Paco_2$, median RR, and median PEEP at time of decannulation to examine an association with mortality, MV duration, and ICU LOS postdecannulation (Table 3). Patients with a PEEP greater than 10 cm H_2O had an ICU LOS of 7.94 days compared with 15.73 days for patients with PEEP less than 10 (Table 3). Patients

TABLE 1.
Baseline Characteristics of the Cohort*

Venovenous ECMO Patients	*n* = 87
Median age (IQR), yr	49 (37–59)
Male, *n* (%)	61 (70)
Median body mass index (IQR)	27.4 (24–34)
Median duration of mechanical ventilation prior to ECMO (IQR), hr	14.9 (6.3–121.2)
Indication, *n* (%)	
ARDS (bacterial pneumonia)	15 (17)
ARDS (viral pneumonia)	20 (23)
ARDS (COVID-19)	4 (4.5)
ARDS (aspiration)	3 (3)
ARDS (other)	13 (15)
Post-lung transplant	8 (9)
Focal lung disease	7 (8)
Hypercapnia/asthma	4 (4.6)
Other	13 (18.4)
Prone ventilation prior to ECMO, *n* (%)	10 (11)
Neuromuscular blockage infusion prior to ECMO, *n* (%)	37 (43)
Nitric oxide/pulmonary vasodilation, *n* (%)	11 (13)
Median lactate prior to ECMO (IQR), mmol/L	1.6 (1.0–2.6)
Median Pao_2:Fio_2 prior to ECMO (IQR)	75.8 (62.9–109.1)
Median $Paco_2$ prior to ECMO (IQR), mm Hg	61 (47.3–76.2)
Median positive end-expiratory pressure prior to ECMO (IQR), cm H_2O	10 (9–15)
25 Fr access canula size, *n* (%)	52 (60)
21 Fr return cannula size, *n* (%)	30 (35)
Femoral-femoral configuration, *n* (%)	48 (56)
Femoral-jugular configuration, *n* (%)	30 (34)
Dual-lumen configuration, *n* (%)	5 (6)
Other configuration, *n* (%)	4 (5)

ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

with a PEEP of 0–5 cm H_2O at decannulation had an ICU LOS of 25.45 days compared with 13.05 days for a PEEP of 6–10 cm H_2O, 7.59 days for a PEEP of 11–15 cm H_2O, 11.50 days for a PEEP of 16–20 cm H_2O, and 8.13 days for a PEEP greater than 20.

DISCUSSION

In this multicenter cohort study of patients receiving VV ECMO, we found statistically significant variation in the physiologic and mechanical ventilator settings at the time of liberation. We found that a higher arterial carbon dioxide and RR at the time of VV ECMO liberation were associated with increased duration of MV postdecannulation and increased duration of ICU stay postdecannulation (Table 4). In contrast, a higher PEEP at decannulation was associated with a decrease in ICU LOS postdecannulation.

Few studies have directly assessed the factors that are important at the time of ECMO decannulation in patients with acute respiratory failure, and currently, there are little data to guide the timing or processes of decannulation from VV ECMO (5, 6, 7, 8, 15). Vasques et al (6) advocated for a stepwise transition from

TABLE 2.
Venovenous Extracorporeal Membrane Oxygenation Outcomes

Outcomes	Value
Duration of VV ECMO, median (IQR), d	9 (5–16)
Duration of VV ECMO in survivors, median (IQR), d	9 (6–14)
Duration of VV ECMO in nonsurvivors, median (IQR), d	12 (4–19)
Duration of mechanical ventilation, median (IQR), d	16 (9–28)
Second VV ECMO run, *n* (%)	0 (0)
Mechanical ventilation during decannulation, *n* (%)	82 (95)
Palliation on ECMO, *n* (%)	21 (24)
Death at 30 d (%)	21 (24)
Death at 90 d (%)	24 (28)

IQR = interquartile range, VV ECMO = venovenous extracorporeal membrane oxygenation.
n = 87 patients on VV ECMO.

TABLE 3.
Comparison of $Paco_2$, Positive End-Expiratory Pressure, and Respiratory Rate Above and Below Median to Study Outcomes

Predictors[a]	Mechanical Ventilation Duration Postdecannulation[b] (d)	*p*	ICU Length of Stay Postdecannulation[b] (d)	*p*
High $Paco_2$ (> 46 mm Hg)	11.67	0.68	12.74	0.95
Low $Paco_2$	9.78		12.49	
High PEEP (> 10 cm H_2O)	6.93	0.10	7.94	0.05
Low PEEP	13.21		15.73	
High RR (> 20 beats/min)	12.17	0.50	14.98	0.17
Low RR	9.02		9.68	

PEEP = positive end-expiratory pressure, RR = respiratory rate.
[a]High was defined as greater than median.
[b]Time from decannulation of venonenous extracorporeal membrane oxygenation (VV ECMO) to outcome.
n = 87 patients on VV ECMO.

membrane lung focused around when the native lung can provide adequate ventilation and oxygenation with a focus of preventing recannulation. Gattinoni et al (7) advocated for a transition from membrane to native lung once the harmful component of MV (Fio_2 and plateau pressures) is mitigated along with monitoring of negative pressure swings in esophageal pressures, which can potentially result in self-induced lung injury. Recently, Al-Fares et al (9) showed that patients with higher TVs, heart rate, ventilatory ratio, and esophageal pressure swings during sweep gas off trials were less likely to achieve safe liberation from VV ECMO defined a priori as avoidance of ECMO recannulation, and increase MV support, need for rescue therapy, or hemodynamic instability within 48 hours after decannulation. Gannon et al conducted a prospective feasibility study in 26 patients highlighting the effectiveness of the use of protocolized daily assessment of readiness of liberation in VV ECMO (10). Both studies focused on liberation from ECMO as the primary outcome and not ICU LOS or liberation from MV (9, 10).

We found that a higher $Paco_2$ and RR at the time of decannulation were associated with longer ICU stay. It is possible that these patients were weaned from the VV ECMO at an earlier stage of their illness when ventilation requirement was still high. At the same time, a higher level of PEEP at decannulation was associated with a shorter ICU LOS. It is possible that maintaining

TABLE 4.

Association of Physiologic and Mechanical Ventilation Settings at Decannulation and Duration of Ventilation or ICU Stay Post Decannulation in Survivors

Decannulation Values	Median (Interquartile Range)	Beta[a] (95% CI)	*p*	Beta[a] (95% CI)	*p*
Pao_2:FIo_2	217 (173–300)	−0.01 (−0.04 to 0.03)	0.93	−0.01 (−0.04 to 0.03)	0.86
$Paco_2$ (mm Hg)	46 (38–48)	0.80 (0.21–1.39)	< 0.01	0.87 (0.33–1.41)	< 0.01
Tidal volume (mL/kg)	6.07 (4.86–7.21)	0.35 (−1.28 to 2.73)	0.47	0.56 (−1.28 to 2.40)	0.53
Respiratory rate (beats/min)	20 (15–22)	1.26 (0.47–2.05)	0.01	1.14 (0.41–1.87)	< 0.01
Positive end-expiratory pressure (cm H_2O)	10 (7.5–12)	−1.34 (−2.87 to 0.19)	0.08	−1.84 (−3.25 to −0.44)	0.01
Peak inspiratory pressure (mm Hg)	24 (20–27)	0.15 (−0.76 to 1.07)	0.74	0.26 (−0.59 to 1.10)	0.54
Dynamic compliance (mL/cm H_2O)	31 (21–40)				
Mechanical ventilation duration post[b] (d)	7 (3–15)				
ICU length of stay post[b] (d)	11 (5–23)				

[a]Denoted multivariable adjusted model including values of age, body mass index, continuous renal replacement therapy, extracorporeal membrane oxygenation (ECMO) duration, mechanical ventilation (MV) duration prior to decannulation, Pao_2:FIo_2 ratio, $Paco_2$, positive end-expiratory pressure, peak inspiratory pressure, pH, respiratory rate, and tidal volume.

[b]Postdecannulation from ECMO.

Survivors at 90 d ($n = 63$) | MV duration post

[b]| ICU length of stay post.

[b]

higher levels of PEEP may be protective for the lung ensuring lung recruitment when oxygenation is transitioned from membrane to native lung (16). We found that no patients required a second run of ECMO, given the ability to turn off gas flow during VV ECMO to effectively evaluate patient stability without VV ECMO, and there are rarely instances of an immediate second VV ECMO run. In addition, in our population, mortality usually resulted from palliation on VV ECMO with a decannulation that was predicted to fail. This contrasts with VA ECMO where low flows can predispose to thrombosis, and therefore, patients are usually not evaluated without full support, and low flows are not maintained for long durations of time, which makes the assessment of weaning and decannulation more crucial (17).

Considering these results, the clinical decision about the timing of VV ECMO decannulation should not only focus on how quickly it is possible to transition back to the ventilator and native lung but instead should potentially also consider which approach decreases time on MV or LOS in intensive care (18). MV may worsen or cause lung injury through VILI (16). VILI is associated with increased pulmonary and systemic inflammatory mediators, which may result in biotrauma and organ dysfunction (19). It may be possible to mitigate the harmful effects of the ventilator with the prolonged use of VV ECMO as it may result in lower TVs and RR (20, 21). A recent physiologic study showed the ability to decrease plasma inflammatory biomarkers by using VV ECMO to minimize the driving pressures generated by the ventilator (22). Our study showed that higher CO_2 and RR values were associated with longer duration of MV and ICU stay postdecannulation. This may suggest differences in recovery of lung mechanics and compliance with ongoing ARDS (19, 20). An approach with late liberation from VV ECMO should likely be associated with weaning of sedation, physiotherapy, and potential extubation prior to decannulation while balancing the risks of circuit-related complications such as bleeding, hemolysis, and infections.

There are several strengths to our study. Data were collected from multiple centers, including major ECMO centers and smaller centers with varying expertise, which increases the generalizability of the findings. Data were collected by trained ICU research coordinators using standard definitions for outcome measures,

and the data were monitored centrally at the research center (Monash University), improving the quality of the data. There were several limitations to the study. The sample size, while large for some ECMO cohort studies, limits our ability to show differences in effect, and the findings likely represent associations and not causation. The study population is heterogeneous in VV ECMO indication and had a low rate of prone ventilation prior to VV ECMO (median duration of MV 14.9 hr prior to VV ECMO), which may limit generalizations. We did not prospectively measure patient's plateau pressure and, thus, were unable to calculate driving pressure. Decannulation and VV ECMO practices were not standardized across all the centers, and we were unable to account for sedation practices in relation to MV weaning and criteria for ICU discharge.

CONCLUSIONS

In patients on VV ECMO, $Paco_2$ and RR at VV ECMO decannulation were associated with increased duration of MV and increased duration of ICU stay postdecannulation. Increased PEEP at decannulation was associated with decreased ICU LOS postdecannulation. These findings may allow clinicians to screen for factors that impact duration of ventilation and ICU stay after ECMO decannulation. Future research should further investigate these associations to establish the optimal ventilator settings and timing of decannulation from VV ECMO. Further studies are needed to understand and define if there exists a patient population that would benefit from prolonged VV ECMO past the point of the ability to make a safe transition to MV to achieve oxygenation and ventilation in order to minimize duration of MV and length of ICU stay.

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