J Crit Care 75 (2023) 154274

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Optimal positive end-expiratory pressure reduces right ventricular dysfunction in COVID-19 patients on venovenous extracorporeal membrane oxygenation: A retrospective single-center study

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ARTICLE INFO

Keywords:
ECMO
Mechanical ventilation
Positive end-expiratory pressure
COVID-19
Manometry

ABSTRACT

While mechanical ventilation practices on venovenous extracorporeal membrane oxygenation (VV ECMO) are variable, most institutions utilize a lung rest strategy utilizing relatively low positive end-expiratory pressure (PEEP). The effect of PEEP titration using esophageal manometry during VV ECMO on pulmonary and cardiac function is unknown. This was a retrospective study of 69 patients initiated on VV ECMO between March 2020 through November 2021. Patients underwent standard PEEP (typically 10 cm H_2O) or optimal PEEP (PEEP titrated to an end-expiratory transpulmonary pressure 0–3 cm H_2O) throughout the ECMO run. The optimal PEEP strategy had higher levels of applied PEEP (17.9 vs. 10.8 cm H_2O on day 2 of ECMO), decreased incidence of hemodynamically significant RV dysfunction (4.55% vs. 44.0%, $p = 0.0001$), and higher survival to decannulation (72.7% vs. 44.0%, $p = 0.022$). Survival to discharge did not reach statistical significance (61.4% vs. 44.0%, $p = 0.211$). In univariate logistic regression analysis, optimal PEEP was associated with less hemodynamically significant RV dysfunction with an odds ratio (OR) of 0.06 (95% confidence interval [CI] = 0.01–0.27, $p = 0.0008$) and increased survival to decannulation with an OR of 3.39 (95% CI 1.23–9.79), $p = 0.02$), though other confounding factors may have contributed.

1. Introduction

Mechanical ventilation practices on veno-venous extracorporeal membrane oxygenation (VV ECMO) have been variable and institution dependent. Most often, ultra-lung protective ventilation (ultra-LPV) with very low tidal volumes and driving pressures, is applied to facilitate “lung rest,” though much variability exists in the definition and application. Importantly, these strategies often default to a positive end-expiratory pressure (PEEP) of 6–10 cm H_2O [1,2].

Right ventricular (RV) dysfunction is a well-known complication of ARDS with an incidence of 30–56% and an associated increase in mortality [3,4]. RV dysfunction in the setting of COVID-19 ARDS has also been noted [5-7] and may be related to an increase in pulmonary vascular resistance in COVID-19 above and beyond non-COVID-19 ARDS [8].

A recent randomized controlled trial in VV ECMO for ARDS found that a ventilation strategy utilizing transpulmonary-pressure (TPP) guided PEEP titration, as compared to a typical lung rest strategy, led to higher rates of successful weaning from ECMO with associated lower driving pressures, mechanical power, and inflammatory markers [9]. Of note, however, this study did not include COVID-19 patients.

At the Oregon Health & Science University (OHSU), we noted a high incidence of RV failure in COVID-19 ARDS patients requiring VV ECMO. Given the potential benefit of an optimized PEEP strategy in VV ECMO patients, in January 2021, we transitioned to an optimal PEEP strategy with the hypothesis that optimal PEEP would be associated with lower rates of RV dysfunction and higher rates of successful weaning from VV ECMO.

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https://doi.org/10.1016/j.jcrc.2023.154274

Available online 8 February 2023

2. Materials and methods

2.1. Study design and setting

This was a retrospective study of all COVID-19 ECMO patients initiated on VV ECMO from March 2020 through November 2021. All patients were hospitalized at OHSU, an academic medical center in Portland, OR with an intensivist-run VV ECMO program that was recently awarded a Platinum Level Center for Excellence Award by the Extracorporeal Life Support Organization (ELSO).

2.2. Intervention

Prior to January 2021, our VV ECMO program routinely utilized pressure control ventilation with an inspiratory pressure of 10 cm H2O, PEEP of 10 cm H2O, and a rate of 10 breaths per minute. Starting in January 2021, our program switched to an optimal PEEP strategy wherein PEEP was titrated daily using esophageal manometry to an end-expiratory transpulmonary pressure of 0–3 cm H2O throughout the ECMO run [10]. In both groups, to ensure compliance with ultra-LPV, if necessary, inspiratory pressure was reduced to achieve a tidal volume of 4 ml/kg of ideal body weight or less.

2.3. Data collection

Retrospective chart review and data collection was performed by two study authors (EE and KJ) under the supervision of the principal investigator (BZ). The study was approved by the OHSU Institutional Review Board (IRB number: 00022803) on 10/11/21. All protected health information (PHI) was stored in a secure identity-authenticated OHSU drive with restricted access, and all institutional IRB procedures were followed in accordance with the ethical standards of the responsible committee and with the Helsinki Declaration of 1975.

2.4. Outcome measures

The primary outcome was the incidence of hemodynamically significant RV dysfunction on echocardiogram (tricuspid annular plane systolic excursion <1.7 cm) requiring inotropic support. Secondary outcomes included ECMO duration, survival to ECMO decannulation, survival to hospital discharge, incidence of barotrauma, and intensive care unit (ICU) and hospital length of stay (LOS).

2.5. Statistical analysis

Continuous variables were compared using Mann-Whitney *U* test while discrete variables were compared using Fischer exact test. A *p* value of <0.05 was considered significant. Additionally, multivariate and univariate logistic regression analyses were used to exam the potential relationship between variables of interest. Statistical analyses were performed utilizing R (v4.0.5) and Prism (v9.0.0, GraphPad, San Diego, CA).

3. Results

Seventy-two patients were identified. Three were excluded with two being transferred immediately after cannulation to other centers given capacity limitations and one dying during cannulation after an arterial injury. Of the 69 included patients, 25 were in the standard PEEP group and 44 in the optimal PEEP group.

Baseline characteristics are shown in Table 1. Of note, the optimal PEEP group was slightly younger than the standard PEEP group and had

Table 1
Baseline characteristics.

Characteristic	All Patients ($n = 69$)	Optimal PEEP Group ($n = 44$)	Standard PEEP Group ($n = 25$)	P Value
Age (yr)	46.6	43.3	52.3	**0.004**
Ethnicity (n, %)	Asian (3, 4.35), Black (3, 4.35), Hispanic (24, 34.8), Native American (4, 5.80), Native Pacific Islander (1, 1.45), White (27, 39.1), Declined (7, 10.1)	Asian (3, 6.81), Black (2, 4.55), Hispanic (11, 25.0), Native American (2, 4.55), White (19, 43.2), Declined (7, 15.9)	Black (1, 4.00), Hispanic (13, 52.0), Native American (2, 4.55), Native Pacific Islander (1, 4.00), White (8, 32.0)	n/a
Male, n (%)	48 (69.6)	28 (63.6)	20 (80.0)	0.184
Body Mass Index, median (kg/m^2)	39.5	42.5	34.2	**0.011**
Murray Score, median	3.75	3.77	3.71	0.373
Comorbidities, n (%)				
Immunocompromised	5 (7.25)	3 (6.82)	2 (8.00)	>0.999
Coronary artery disease	0 (0)	1 (2.27)	0 (0)	>0.999
Hypertension	15 (21.7)	9 (20.5)	6 (24.0)	0.767
Diabetes Mellitus	20 (29.0)	13 (29.5)	7 (28.0)	>0.999
Chronic Kidney Disease	2 (2.90)	2 (4.55)	0 (0)	0.531
Pre-ECMO support				
HFNC, n (%)	56 (81.2)	35 (79.5)	21 (84.0)	0.756
NIPPV, n (%)	28 (40.6)	19 (43.2)	9 (36.0)	0.617
Pre-ECMO ventilator days	3.38	3.93	2.40	0.165
Pre-ECMO proning, n (%)	64 (92.8)	42 (95.5)	22 (88.0)	0.344
Paralytics, n (%)	65 (94.2)	42 (95.5)	23 (92.0)	0.617
Vasopressor, n (%)	40 (58.0)	26 (59.1)	14 (56.0)	0.806
Ventilator mode (n, %)	VC (54, 78.3), APRV (7, 10.1), PC (3, 4.35), VDR (1, 1.45), Undocumented (4, 5.80)	VC (36, 81.8), APRV (3, 6.82), PC (2, 4.55), VDR (0,0), Undocumented (3, 6.82)	VC (18, 72.0), APRV (4, 16.0), PC (1, 4.00), VDR (1, 4.00), Undocumented (1, 4.00)	n/a
ABG prior to cannulation				
pH	7.26	7.26	7.26	0.423
pCO2 (mmHg)	68.4	70.1	65.2	0.240
pO2 (mm Hg)	73.9	68.7	83.1	0.160
Bicarbonate (mEq/L)	29.6	30.4	28.1	0.210

ECMO = extracorporeal membrane oxygenation, HFNC = high-flow nasal cannula, NIPPV = noninvasive positive pressure ventilation, ABG = arterial blood gas, VC = volume control, APRV = airway pressure release ventilation, PC = pressure control, VDR = volumeric diffusive respirator. Bold values are those with a significant p value.

a higher BMI. Comorbidities, pre-ECMO noninvasive support, ventilator days, adjunctive therapies, and arterial blood gas values were otherwise similar.

ECMO run variables are shown in Table 2. Of note, ECMO blood and gas flows were similar between groups. The optimal PEEP group had significantly higher PEEP levels at day 2 (17.9 vs. 10.8 cm H_2O, $p \leq 0.0001$) with levels being similar by day 7. Driving pressure was similar between groups throughout the ECMO run. There were higher rates of extubation and reintubation in the standard PEEP group and more patients in the optimal PEEP group underwent prone positioning after cannulation.

Primary and secondary outcomes are listed in Table 3. Notably, the optimal PEEP group had significantly reduced rates of hemodynamically significant RV dysfunction (4.5% vs. 44.0%, $p = 0.0001$) and higher rates of survival to decannulation (72.7% vs. 44.0%, $p = 0.022$).

We did not find a significant difference in survival to discharge of the optimal PEEP group relative to the standard PEEP group. Additionally, there was no difference in ECMO duration with an average run of approximately 22 days in both groups and no difference in ICU or hospital LOS.

Table 2
ECMO run variables.

ECMO run variables	All patients (n = 69)	Optimal PEEP group (n = 44)	Standard PEEP group (n = 25)	P value
Mean PEEP on ECMO day 2 (cm H_20)	15.3	17.9	10.8	**<0.0001**
Mean PEEP on ECMO day 7 (cm H_20)	13.4	14.1	11.5	0.079
Mean driving pressure on ECMO day 2 (cm H_20)	9.37	9.53	10.2	0.665
Mean driving pressure on ECMO day 7 (cm H_20)	10.5	10.6	10.1	0.370
Sedative infusion at ECMO day 2, n (%)	55 (79.7)	37 (84.1)	18 (72.0)	0.350
Mean RASS at ECMO day 2	−2.16	−2.27	−1.96	0.219
Sedative infusion at ECMO day 7, n (%)	48 (69.6)	36 (81.8)	12 (48.0)	**0.006**
Mean RASS at ECMO day 7	−1.66	−1.76	−1.48	0.365
Mean ECMO RPM at 48 h	3159	3131	3208	0.855
Mean ECMO blood flow at 48 h (L/min)	4.26	4.32	4.15	0.558
Mean ECMO sweep gas flow at 48 h (L/min)	6.62	6.70	6.48	0.923
Mean ECMO F_SO_2 at 48 h	89.9	85.3	98.0	**0.001**
Extubated on ECMO, n (%)	21 (30.4)	3 (6.82)	18 (72.0)	**<0.0001**
Reintubated, n (%)	12 (17.4)	2 (4.55)	10 (40.0)	**0.0004**
Tracheostomy, n (%)	35 (50.1)	24 (54.5)	11 (44.0)	0.458
VTE, n (%)	37 (53.6)	25 (56.8)	12 (48.0)	0.616
Vasopressors, n (%)	59 (85.5)	40 (90.9)	19 (76.0)	0.152
CRRT, n (%)	37 (53.6)	25 (56.8)	12 (48.0)	0.616
Proning on ECMO, n (%)	10 (14.5)	10 (22.7)	0 (0)	**0.011**
Post-cannulation culture data positivity				
Blood, n (%)	29 (42.0)	20 (45.5)	9 (36.0)	0.612
Urine, n (%)	13 (18.8)	8 (18.2)	5 (11.36)	>0.999
Sputum, n (%)	54 (78.3)	35 (79.5)	19 (76.0)	0.767

PEEP = positive end-expiratory pressure, ECMO = extracorporeal membrane oxygenation, RASS = Richmond Agitation Sedation Scale, RPM = rotations per minute, F_SO2 = oxygen fraction of the sweep gas, VTE = venous thromboembolism, CRRT = continuous renal replacement therapy. Bold values are those with a significant p value.

Table 3
Primary and secondary outcomes.

Outcome	All patients (n = 69)	Optimal PEEP group (n = 44)	Standard PEEP group (n = 25)	P Value
Primary Outcome				
RV dysfunction post-cannulation, n (%)	13 (18.8)	2 (4.55)	11 (44.0)	**0.0001**
Secondary outcomes				
Survival to decannulation, n (%)	43 (62.3)	32 (72.7)	11 (44.0)	**0.022**
Survival to discharge, n (%)	38 (55.1)	27 (61.4)	11 (44.0)	0.211
Barotrauma on ECMO, n (%)	23 (33.3)	16 (36.4)	7 (28.0)	0.598
Pneumothorax	13 (18.8)	9 (20.5)	4 (16.0)	0.756
Chest tube inserted	10 (14.5)	7 (15.9)	3 (12.0)	0.737
ECMO duration (days)	22.0	22.0	21.9	0.497
ICU LOS (days)	28.84	30.43	26.32	0.174
Hospital LOS (days)	38.88	40.82	35.48	0.553
Discharge location (n, %)	Home (22, 31.9), SNF (14, 20.3), Transfer (2, 2.90)	Home (15, 34.1), SNF (10, 22.7)	Home (7, 28.0), SNF (4, 16.0), Transfer (2, 8.00)	
Overall mortality, n (%)	31 (44.9)	17 (38.6)	14 (56.0)	0.211

RV = right ventricular, ICU = intensive care unit, ECMO = extracorporeal membrane oxygenation, SNF = skilled nursing facility. Bold values are those with a significant p value.

Logistic regression results are shown in Table 4. Univariate logistic regression identified that optimal PEEP was associated with hemodynamically significant RV dysfunction with an odds ratio (OR) of 0.06 (95% confidence interval [CI] = 0.01–0.27, $p = 0.0008$) and survival to decannulation with an OR of 3.39 (95% CI 1.23–9.79), $p = 0.02$). Multivariate logistic regression examining the effect of optimal PEEP after accounting for the effects of age, history of hypertension and diabetes, and date of hospital admission on onset of RV dysfunction were also significant with an OR of 0.07 (95% CI = 0.004–0.47, $p = 0.02$).

Table 4
Logistic regression analysis between optimal PEEP and outcomes.

Variables	Univariate odds ratio (95% CI)	P value	Multivariate odds ratio (95% CI)	P value
Primary Outcome				
RV dysfunction-post-cannulation	0.06 (0.01–0.27)	**0.0008**	0.07 (0.004–0.47)	**0.02**
Secondary Outcomes				
Survival to decannulation	3.39 (1.23–9.79)	**0.02**	2.86 (0.75–12.06)	0.13
Survival to discharge	2.02 (0.75–5.58)	0.17	1.94 (0.50–8.13)	0.34
Barotrauma on ECMO	0.49 (0.14–1.62)	0.24	0.86 (0.20–3.52)	0.84

In multivariate analysis, the following factors were considered: age, history of hypertension, history of diabetes, admission to hospital after 7/1/2021 (when most patients were infected with the Delta variant). PEEP = positive end-expiratory pressure, CI = confidence interval, RV = right ventricular ICU = intensive care unit, ECMO extracorporeal membrane oxygenation. Bold values are those with a significant p value.

4. Discussion

In this retrospective review of COVID-19 VV ECMO patients at a single institution, an optimal PEEP strategy was associated with significantly reduced rates of hemodynamically significant RV dysfunction and improved survival to decannulation when compared to a standard PEEP strategy. However, these results must be considered alongside a few important potential confounders in this study – namely, increased rates of proning in the optimal PEEP group in addition to increased BMI cohort (a population in which use of esophageal manometry is likely to be of the highest benefit).

PEEP has several theoretical beneficial effects in ARDS, including reducing ventilation/perfusion mismatch and avoiding alveolar collapse, thus improving oxygenation and respiratory system compliance [11]. This improvement in pulmonary vascular resistance (PVR) may reduce the afterload imposed on the RV [12,13]. While it makes physiologic sense that reducing PVR, and thus RV afterload, by optimizing PEEP may reduce the incidence of RV dysfunction, the optimal level of PEEP in ARDS remains unclear and a higher PEEP strategy has not reduced mortality relative to a lower PEEP strategy [14]. Our findings are consistent with previously published data on the incidence of RV dysfunction in ARDS, its negative effect on mortality, and the potentially beneficial effects of optimized PEEP on ECMO survival [3-7,9].

While we did not find a significant difference in the survival to discharge of the optimal PEEP group relative to the standard PEEP group, it is noteworthy that the optimal PEEP group was treated later in the pandemic, a time during which the global survival of patients with COVID-19 on VV ECMO were declining [15-20]. This variation may relate to changes in viral strains and it is unclear how this impacts interpretation of our data. Similarly, a German cohort study demonstrated worsening mortality over the period from March 2020 to September 2021 – a time frame that coincides with our study period [16]. Several other centers also reported worsening mortality over a similar period during the pandemic [17-19]. A recent meta-analysis seems to confirm this trend of worsening ECMO mortality throughout the course of the pandemic [20].

This study has several important limitations. First, this is a single-center study and is retrospective in nature. Second, while the correlation between optimal PEEP and decreased incidence of RV dysfunction, and potentially increased survival, is consistent with the previously mentioned publications, this study cannot prove causality. Additionally, proning while on ECMO was incorporated into our program's practice near the end of the study period, accounting for the difference in prone position rates between the standard and optimal PEEP groups. Given retrospective data suggestive of improved outcomes with prone positioning during VV ECMO [21], we are unable to rule out the potential impact of this intervention on our results, and specifically on the reduced rates of RV dysfunction. Additionally, the optimal PEEP cohort had a higher BMI, a population in which esophageal manometry might yield the greatest benefit given the limitations of typical PEEP-titration methods in the setting of reduced chest wall compliance. Controlled prospective studies are needed to better elucidate these findings.

In summary, this single-center retrospective study suggests that for patients with COVID-19 on VV ECMO, an optimal PEEP strategy is associated with a reduced incidence of hemodynamically significant RV dysfunction and improved survival to decannulation. However, there are several important limitations to consider in the interpretations of these results and further studies are needed to confirm these findings.

Disclosures

We have no financial disclosures or conflicts of interest to report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Ethan M. Estoos: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Kevin P. Jocham:** Investigation, Writing – original draft, Data curation. **Chengda Zhang:** Formal analysis, Investigation, Writing – original draft. **Lauren M. Benson:** Conceptualization, Methodology, Data curation, Writing – review & editing. **Anamaria Milas:** Conceptualization, Methodology, Data curation, Writing – review & editing. **Bishoy Zakhary:** Conceptualization, Methodology, Writing – review & editing, Visualization, Supervision.

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