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<https://escholarship.org/uc/item/3bp682gq>

Journal

Journal of Cardiothoracic and Vascular Anesthesia, 37(3)

ISSN

1053-0770

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Publication Date

2023-03-01

DOI

10.1053/j.jvca.2022.11.033

Peer reviewed



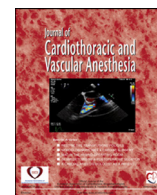
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Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Original Article

Very Low Driving-Pressure Ventilation in Patients With COVID-19 Acute Respiratory Distress Syndrome on Extracorporeal Membrane Oxygenation: A Physiologic Study

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Objectives: To determine in patients with acute respiratory distress syndrome (ARDS) on venovenous extracorporeal membrane oxygenation (VV ECMO) whether reducing driving pressure (ΔP) would decrease plasma biomarkers of inflammation and lung injury (interleukin-6 [IL-6], IL-8, and the soluble receptor for advanced glycation end-products sRAGE).

Design: A single-center prospective physiologic study.

Setting: At a single university medical center.

Participants: Adult patients with severe COVID-19 ARDS on VV ECMO.

Interventions: Participants on VV ECMO had the following biomarkers measured: (1) pre-ECMO with low-tidal-volume ventilation (LTVV), (2) post-ECMO with LTVV, (3) during low-driving-pressure ventilation (LDPV), (4) after 2 hours of very low driving-pressure ventilation (V-LDPV, main intervention $\Delta P = 1$ cmH₂O), and (5) 2 hours after returning to LDPV.

Mazen F. Odish, MD, is currently supported by a grant (T32GM121318) from National Institute of General Medical Sciences, National Institute of Health (NIH). Angela Meier, MD, PhD, is currently supported by a grant (1KL2TR001444) by the Altman Clinical and Translational Research Institute (ACTRI) at the University of California, San Diego. The ACTRI is funded from awards (UL1TR0001442) issued by the National Center for Advancing Translational Sciences, NIH. She also received support from a supplement of R01HL137052 (PI: Crotty Alexander). Mark Hepokoski, MD, is supported by the Department of Veterans Affairs CDA-2 IK2BX004338-01 and an American Thoracic Society Research Program Unrestricted Critical Care Grant. Laura Crotty Alexander, MD, is supported by grants from the NHLBI (R01HL137052), Department of Veterans Affairs (1I01BX004767), and the Tobacco-Related Disease Research Program (T30IP0965). Tatum S. Simonson, PhD, is currently supported by a grant (R01HL145470) from the NIH. Atul Malhotra, PhD, is principal investigator or co-investigator on NIH RO1 HL085188, K24 HL132105, T32 HL134632, RO1 HL154026; R01 AG063925; R01 HL148436, RO1 HL 119201, RO1 HL081823, RO1 HL 142114, UG1 HL139117-01, CPLGO (Center for Physiological Genomics of Low Oxygen), RO1 CA215405, RO1 HL133847. He reports medical education income from LivaNova, Equilibrium and Corvus. The content is solely the responsibility of the authors and does not necessarily represent the official view of the NIH. Robert Owens, MD, is currently supported by a grant (R01HL142114) from NHLBI, NIH.

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<https://doi.org/10.1053/j.jcva.2022.11.033>

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Main Measurements and Results: Twenty-six participants were enrolled; 21 underwent V-LDPV. There was no significant change in IL-6, IL-8, and sRAGE from LDPV to V-LDPV and from V-LDPV to LDPV. Only participants (9 of 21) with nonspontaneous breaths had significant change ($p < 0.001$) in their tidal volumes (V_t) (mean \pm SD), 1.9 ± 0.5 , 0.1 ± 0.2 , and 2.0 ± 0.7 mL/kg predicted body weight (PBW). Participants with spontaneous breathing, V_t were unchanged— 4.5 ± 3.1 , 4.7 ± 3.1 , and 5.6 ± 2.9 mL/kg PBW ($p = 0.481$ and $p = 0.065$, respectively). There was no relationship found when accounting for V_t changes and biomarkers.

Conclusions: Biomarkers did not significantly change with decreased ΔP s or V_t changes during the first 24 hours post-ECMO. Despite deep sedation, reductions in V_t during V-LDPV were not reliably achieved due to spontaneous breaths. Thus, patients on VV ECMO for ARDS may have higher V_t (ie, transpulmonary pressure) than desired despite low ΔP s or V_t .

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Key Words: acute respiratory distress syndrome; biomarkers; COVID-19; low driving pressure ventilation; extracorporeal membrane oxygenation; ventilator-induced lung injury

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) is a common and deadly condition for which many patients require invasive mechanical ventilation. Although mechanical ventilation may be lifesaving, the repetitive stress and strain imposed on the lung parenchyma may worsen lung injury—known as "ventilator-induced lung injury" (VILI).¹ Ventilator-induced lung injury and the underlying ARDS etiology precipitate the systemic release of inflammatory mediators that worsen lung injury and contribute to multiorgan injury, a phenomenon known as "biotrauma".² Thus, decreasing VILI and the associated biotrauma is a cornerstone of ARDS treatment. Low-tidal-volume ventilation (LTVV), with 6 mL/kg (with plateau pressure [pplat] ≤ 30 cmH₂O) compared to 12 mL/kg of predicted body weight (PBW), is associated with reduced mortality.³ The benefit of LTVV is likely greatest in patients with the highest elastance and/or lowest compliance.⁴ Amato et al. analyzed data from multiple ARDS studies that showed lower driving pressure (ΔP) was associated independently with improved survival. Importantly, there was no clear threshold below which further reductions in ΔP (and tidal volumes) did not result in further reductions in mortality.⁵ However, it should be noted that higher driving pressure also may reflect decreased compliance due to more severe ARDS, resulting in higher mortality.⁶

For the most severe cases of ARDS, extracorporeal membrane oxygenation (ECMO) maybe required to maintain adequate gas exchange.^{7,8} Extracorporeal membrane oxygenation can control the partial pressure of oxygen and carbon dioxide levels in the blood, but optimal ventilator settings during ECMO remain unclear.⁹ The Extracorporeal Life Support Organization (ELSO) has recommended ventilator guidelines that limit ΔP to 10-to-15 cmH₂O to maintain inspiratory pplat ≤ 25 cmH₂O, positive end-expiratory pressure (PEEP) of ≥ 10 cmH₂O, and respiratory rates of 4-to-15 breaths/min.¹⁰ These ELSO guidelines are referred to as low-driving-pressure ventilation (LDPV). Extracorporeal membrane oxygenation could further allow clinicians to use ventilator settings lower than LDPV; for example, setting ΔP at 1 or 0 cmH₂O. Such an approach may offer additional lung protection, as animal data show that very low ΔP , including "apneic" or zero ΔP , decreases histologic markers of lung injury.^{11,12}

Multiple plasma biomarkers have been used to measure VILI and/or biotrauma.¹³ Some systemic proinflammatory biomarkers include interleukin-6 (IL-6) and IL-8. They also may be relatively organ-specific, such as soluble receptors for

advanced glycation end-products (sRAGE), an epithelial marker of lung injury.¹³ Prior reports have demonstrated rapid (within 1 hour) changes in biomarkers with tidal volume (V_t) changes.¹⁴ Biomarkers (specifically, sRAGE, IL-6, and IL-8) have been shown to prognosticate patients with ARDS on ECMO and may be used as a surrogate for VILI and/or biotrauma to evaluate the effects of different ventilator settings.¹⁴⁻¹⁶ It should be noted that there are reports of extracorporeal support (eg, ECMO, cardiopulmonary bypass, etc) inducing systemic inflammation and corresponding biomarkers, specifically IL-6.^{17,18}

The study authors sought to test the hypothesis that for patients with ARDS on ECMO, decreasing lung stretch via very LDPV (V-LDPV) would decrease blood biomarkers of inflammation and lung injury (IL-6, IL-8, and sRAGE).

Materials and Methods

Study Design

This was a prospective cohort study. Enrollment was from March 1, 2020 to November 1, 2020. No power calculation was performed as this study was an exploratory pilot study, and the number of participants was based on feasibility and existing literature.^{15,16} The study protocol was approved by the institutional review board. Informed consent was obtained from each participant's healthcare proxy, according to the authors' institutional guidelines.

Participants

The inclusion criteria were as follows: (1) age > 18 years, (2) planned initiation of VV-ECMO support, (3) severe ARDS defined by the Berlin criteria, and (4) mechanical ventilation.¹⁹ The exclusion criteria were as follows: (1) solid organ transplantation, (2) hemodynamic instability defined as mean arterial pressure (MAP) < 65 mmHg despite vasopressors and fluid administration, or (3) expected survival < 24 hours. Patients with COVID-19 with obvious cardiac dysfunction (eg, by echocardiogram or need for high-dose vasopressors) were not offered ECMO in the authors' county due to the pandemic surge and resulting resource limitations during study enrollment (pressor requirements at ECMO initiation are shown in Table 1).²⁰⁻²²

Table 1
Patient Demographics and Outcomes

	All Participants	Participants Underwent V-LDPV Protocol	V-LDPV (Survivors)	V-LDPV(Non-survivors)
Total	25	21	9	12
Patient demographics				
Male, n (%)	21 (84)	17 (80.9)	7 (77.8)	10 (83.3)
Age, mean ± SD, y	50.1 (9.5)	51 (9.7)	48 (9.8)	53.3 (9.3)
Race, n (%)				
White	23 (92)	19 (90.5)	8 (88.9)	11 (91.7)
Asian	1 (4)	1 (4.8)	1 (11.1)	0
Other/mixed race	1 (4)	1 (4.8)	0	1 (8.3)
Hispanic	23 (92)	20 (95.2)	9 (100)	11 (91.7)
BMI, mean ± SD, kg/m ²	31.4 (4.8)	31.7 (4.7)	32.2 (4.8)	31.3 (4.8)
Past medical history, n (%)				
Any respiratory disease*	5 (20)	5 (23.8)	3 (33.3)	2 (16.7)
Type 2 diabetes	8 (32)	8 (38.1)	3 (33.3)	5 (41.7)
Pregnant or postpartum	2 (8)	2 (9.5)	2 (22.2)	0
Malignancy	1 (4)	1 (4.8)	0	1 (8.3)
ARDS from COVID-19, n (%)	25 (100)	-	-	-
SOFA score at ICU admission, mean ± SD	9.7 (2.6)	9.8 (2.8)	9.3 (2.7)	10.2 (3)
Norepinephrine equivalent prior to V-LDPV, μg/kg/min, mean ± SD		0.09 (0.1)	0.09 (0.09)	0.11 (0.11)
Pre-ECMO ventilator settings, mean ± SD [†]				
	n = 15			
Respiratory rate, breaths/min	28 (4.9)			
Tidal volume, mean ± SD, mL/kg of PBW	6.2 (1.5)			
PEEP, cmH ₂ O	12.6 (4.1)			
Plateau pressure, cmH ₂ O	28.6 (5.5)			
Driving pressure, cmH ₂ O	16 (5.4)			
Mean airway pressure, mean ± SD, cmH ₂ O	20 (4.58)			
Mechanical power, mean ± SD, joules/min	29.8 (8.57)			
F _i O ₂	0.94 (0.15)			
Compliance of the respiratory system, mean ± SD, mL/cmH ₂ O	25.3 (10.7)			
PaO ₂ /F _i O ₂ , mean ± SD	93 (30)	89 (27)	88 (16)	89 (32)
Neuromuscular blockade, n (%)	13 (86.6)	6 (28.5)	2 (22.2)	4 (33.3)
Intubation time prior to ECMO, mean ± SD, d	6.3 (4.4)	5.2 (3.3)	5.4 (4.1)	5 (2.7)
ECMO time prior V-LDPV, median (IQR), h	-	17 (14-20)	16 (14-19.3)	17 (14.5-19.3)
Mobile ECMO, n (%)	10 (40)	10 (47.6)	5 (55.6)	5 (41.7)
ECMO circuit settings prior to V-LDPV [‡]				
Blood flow, mean ± SD, L/min		4.8 (0.6)		
Oxygenator sweep gas, mean ± SD, L/min		4.5 (2)		
Venous pressure, mean ± SD, mmHg		-94.1 (28.9)		
End-expiratory transpulmonary pressure gradient, mean ± SD, cmH ₂ O [§]		-0.5 (4.3)		
Clinical course				
Duration of ECMO support, mean ± SD, d	25.5 (17.8)	26.9 (18.2)	23.1 (15.6)	29.8 (20.1)
Ventilator Associated Pneumonia, n (%)	21 (84)			
Length of hospital stay, mean ± SD, d	41 (21.6)	40.43 (24.7)	41.44 (17.2)	39.7 (25.3)
Tracheostomy placement during hospitalization, n (%)	10 (40)	9 (42.9)	5 (55.6)	4 (33.3)
Renal replacement therapy during hospitalization, n (%)	2 (8)	2 (9.5)	0	2 (16.7)
Intracerebral hemorrhage during hospitalization, n (%)	3 (12)	3 (14)	0 (0)	3 (25)
Survival to hospital discharge, n (%)	13 (52)	9 (42.9)	9	0

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic pulmonary pulmonary disease; ECMO, extracorporeal membrane oxygenation; F_iO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment; V-LDPV, verylow driving-pressure ventilation.

* Respiratory diseases included asthma and COPD.

[†] Missing ventilator settings from 10 participants due to mobile ECMO cannulation.

[‡] ECMO settings during sample collections.

[§] Nineteen of the 21 participants that underwent V-LDPV had an esophageal manometer placed.

Some participants had “mobile” ECMO, i.e., had VV-ECMO initiated at another hospital by the authors’ ECMO team prior to transfer.^{23,24} The ECMO configuration, equipment, and settings can be found in the supplement.

Data Collection

Demographic information, baseline characteristics, ventilator, hemodynamics and vasopressors and/or inotropes, analgesia and sedative medication doses, neuromuscular blockade (NMB) use, and laboratory values were collected at study enrollment and during protocol sample collection. The norepinephrine equivalent dose and mechanic work were calculated as previously reported (see equations in supplemental materials).^{25,26}

Experimental Protocol

The study authors measured plasma biomarkers at the following time points: (1) pre-ECMO with LTVV, (2) post-ECMO with LTVV, (3) post-ECMO with LDPV, (4) post-ECMO after 2 hours of V-LDPV (main intervention), and (5) post-ECMO 2 hours after returning to LDPV from V-LDPV (main intervention) (Fig 1; Supplemental Table S1). Very low driving-pressure ventilation was performed for 2 hours with a ΔP of 1 cmH₂O. The ventilators were set to pressure-control ventilation during LDPV and V-LDPV. All measurements were made with participants in the supine position, with the head of the bed elevated at 20°-to-40°. An esophageal balloon (Cooper Surgical) was placed prior to the V-LDPV protocol, as previously described.²⁷

Patients were frequently on NMB at the time of ECMO cannulation and deeply sedated at the time of all measurements. After the initiation of ECMO, the decision to continue or stop NMB was left to the clinical team (and was sometimes stopped to obtain a neurologic examination). No patients during the protocol (V-LDPV) had a spontaneous awaking or breathing trial or were placed in the prone position. Standard intensive care unit therapies for patients with ARDS at the authors’

institution, such as stress ulcer prophylaxis, sedation, analgesia, and restrictive fluid management, were provided and unchanged by their protocol. Given the brief duration of the protocol and the within-subjects comparisons, the authors doubt these had a major impact on their results.

Blood Analysis

All blood samples were drawn into heparin plasma separator tubes (Becton, Dickinson and Co) and centrifuged within 2 hours of collection at 2,000 × g for 15 minutes. Plasma was aliquoted and stored at -80°C within 2.5 hours of collection. The IL-6, IL-8, sRAGE, chemokine ligand-5 (CCL-5), angiopoietin-2, angiopoietin-1, interferon γ-inducible protein-10, tumor necrosis factor α, CCL-2, CCL-9, interleukin 10 (IL-10), and vascular endothelial growth factor levels were measured in 2-fold diluted plasma using a BioLegend Legendplex multiplex custom cytokine panel. Biomarker values were calculated using Biologend’s cloud-based analysis software.

Outcomes

The primary outcome was the changes in plasma IL-6, IL-8, and sRAGE between periods of LDPV and V-LDPV. The secondary outcomes included the following: tolerability and safety of V-LDVP as assessed by MAP, heart rate, pulse oximetry, norepinephrine equivalent dose, ECMO circuit blood flow rate, and ECMO sweep gas flow rate, and changes in additional biomarker levels (ie, CCL-5, angiopoietin-2, angiopoietin-1, interferon-inducible protein-10, tumor necrosis factor α, CCL-2, CCL-9, IL-10, and vascular endothelial growth factor).

Statistical Analysis

Descriptive statistics were calculated using mean (SD) or median (IQR) for the continuous variables and frequency (percentage) for the categorical variables.

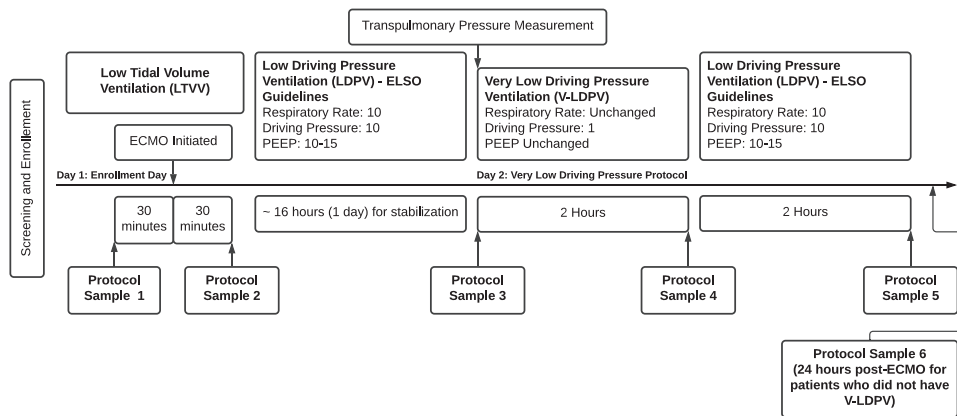


Fig 1. Study protocol. The ventilators were set to pressure-control ventilation during low-driving-pressure ventilation and very low driving-pressure ventilation; thus, plateau pressure = positive end-expiratory pressure + driving pressure. May reference Supplementary Table S1 in Supplemental Appendix for protocol sample timing and ventilator settings. ELSO, extracorporeal life support organization; EMCO, extracorporeal membrane oxygenation; LDPV, low-driving-pressure ventilation; LTVV, low-tidal-volume ventilation; PEEP, positive end-expiratory pressure; V-LDPV, very low driving- pressure ventilation.

The primary analyses assessed the change in V_t and each biomarker level from LDPV (protocol sample 3) to V-LDPV (protocol sample 4) and from V-LDPV back to LDPV (protocol sample 5). Linear mixed-effects models were used with V_t or biomarker levels (in log scale) at each time point as the outcome, sampling time as the fixed effect, and random intercept and slope. The authors also studied whether spontaneous breathing affected the change in V_t or biomarker levels by including the interaction term of spontaneous breathing and sampling time as a fixed effect in the models. Spearman's correlations were calculated to assess whether a change in V_t from LTVV to LDPV (protocol sample 1 to 3), LDPV to V-LDPV (protocol sample 3 to 4), and from V-LDPV to LDPV (protocol sample 4 to 5) was associated with the change in biomarkers.

To determine if the initiation of ECMO impacted biomarker levels, paired t tests were used to assess the change in biomarker levels between protocol samples 1 and 2. To study the effects of ECMO over the first 16-to-24 hours, the authors looked at the change in biomarker levels between protocol samples 1 (on LTVV) and 3 (on ECMO for participants who performed V-LDVP protocol), or 6 (on ECMO for participants who did not perform V-LDVP protocol). Given the number of biomarkers the authors examined, the Benjamini-Hochberg method was used to adjust for multiple testing. Statistical analysis was performed with SPSS (version 27.0; IBM SPSS, Inc, Armonk, NY) and R (version 3.6.1; R Foundation for Statistical Computing) statistics software.

Results

Participants

Twenty-six participants were enrolled. One participant was discovered to have an intracerebral hemorrhage immediately after ECMO initiation, and support was withdrawn shortly thereafter and not included in the analysis. Sixteen patients were initiated on ECMO at the authors' institution; whereas 10 were begun prior to transfer to their institution (mobile ECMO), and most (9 of 10 [90%]) of these participants did not

have protocol samples 1 and 2 (Supplemental Figure S1). Twenty-one participants underwent the V-LDPV intervention. Four participants only had protocol samples 1, 2, and 6 collected (without V-LDPV), due to the initial COVID-19 pandemic restrictions on the biosafety level-2 laboratory operating hours and staff availability. One participant's V-LDPV protocol used a ΔP of 5 cmH₂O due to the specific ventilator model limitations on minimal ΔP .

Patient Demographics and Clinical Course

Baseline demographics are reported in Table 1. All participants had ARDS due to SARS-CoV-19. Three participants had intracerebral hemorrhages and did not survive to hospital discharge. Thirteen (13 of 25 [52%]) participants survived to hospital discharge; of the participants (n = 21) who underwent the V-LDPV protocol, 9 (9 of 21 [43%]) survived (Table 1).

Very Low Driving-Pressure Ventilation

In 21 participants, the mean V_t going from LDPV to V-LDPV and back to LDPV was 3.4 ± 2.6 to 2.7 ± 3.2 to 4.0 ± 2.9 mL/kg PBW ($p = 0.075$ from LDPV to V-LDPV; $p < 0.001$ from V-LDPV back to LDPV; Fig 2). Four patients were on NMB during V-LDPV and did not have spontaneous respirations based on esophageal manometry changes and respiratory rate. Additionally, 5 patients not on NMB also had no evidence of spontaneous respiration. The V_t of these 9 participants was changed significantly from LDPV to V-LDPV ($p < 0.001$) and from V-LDPV back to LDPV ($p < 0.001$) with V_t of 1.9 ± 0.5 , 0.1 ± 0.2 , and 2.0 ± 0.7 mL/kg PBW, respectively.

Twelve participants (12 of 21 [57%]) had spontaneous respirations. The V_t in these participants did not significantly change from LDPV to V-LDPV ($p = 0.481$) and from V-LDPV back to LDPV ($p = 0.065$) with V_t of 4.5 ± 3.1 to 4.7 ± 3.1 to 5.6 ± 2.9 mL/kg PBW.

There were no significant changes in safety parameters, including MAP, heart rate, pulse oximetry, norepinephrine equivalent dose, ECMO circuit blood flow rate, and ECMO

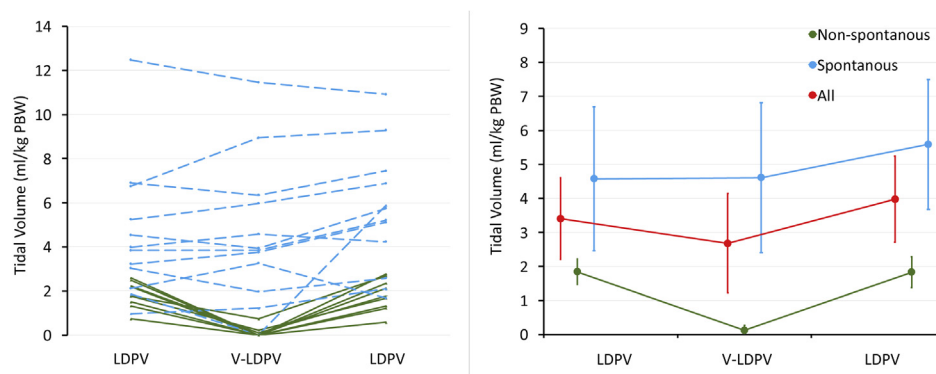


Fig 2. Tidal volume changes during experimental ventilator protocol. Left panel, tidal volumes per kg of predicted body weight in all participants (n = 21) undergoing very low driving-pressure ventilation. Blue dashed lines are spontaneously breathing participants (n = 12). Green solid lines are nonspontaneously breathing participants (n = 9). Right panel, average tidal volumes per kg of predicted body weight. The Red line is all participants, blue line is spontaneously breathing participants, and green line is nonspontaneously breathing participants. Error bars represent 95% CI. LDPV, low-driving-pressure ventilation; PBW, predicted body weight; V-LDPV, very low driving-pressure ventilation.

sweep gas flow rate during the V-LDPV protocol (Supplemental Table S2).

Biomarker Outcomes

There were no significant changes in primary biomarkers (sRAGE, IL-6, IL-8) from LDPV (protocol sample 3) to V-LDPV (protocol sample 4) and back to LDPV (protocol sample 5) (Table 2; Fig 3). Patients who were spontaneously breathing had higher biomarkers levels, although this was not statistically significant (Fig 3). There was no significant association between changes in V_t and biomarkers (sRAGE, IL-6, IL-8) from LTVV to LDPV and from LDPV to V-LDPV (Supplemental Figure S2).

The primary biomarkers (sRAGE, IL-6, IL-8) did not have significant changes from pre-ECMO (protocol sample 1: LTVV) to immediately post-ECMO (protocol sample 2: LTVV) for the 14 patients who had both samples (Table 2; Supplemental Table S3).

In addition, sRAGE, IL-6, and IL-8 did not significantly change from pre-ECMO (protocol sample 1: LTVV) compared to 16 hours and 24 hours post-ECMO (protocol sample 3: LDPV and protocol sample 6: LDPV, respectively) (Table 2; Supplemental Table S4). Sixteen participants with protocol sample 1 were included in this analysis. The study authors found no relationship among their main biomarkers (IL-6, IL-10, and sRAGE) and survivors versus nonsurvivors in a logistic regression ($p = 0.280$, $p = 0.086$, $p = 0.357$, respectively). All other biomarkers that did change significantly during the authors' protocol are noted in Table 2.

Discussion

The authors tested the hypothesis that V-LDPV would lead to decreased levels of biomarkers of lung injury and inflammation in participants with COVID-19 ARDS on ECMO. They found that V-LDPV was feasible and safe, but it did not uniformly result in very low V_t (<4 mL/kg of PBW) due to

Table 2
Biomarkers Measurements at Protocol Samples 1-6

PlasmaBiomarker	Protocol Sample 1: Pre-ECMO With LTVV (n = 16)	Protocol Sample 2: Post-ECMO With LTVV (n = 14)	Protocol Sample 3: Post-ECMO With LDPV (n = 22)	Protocol Sample 4: Post-ECMO After 2 Hours of V-LDPV (n = 21)	Protocol Sample 5: Post-ECMO With LDPV (n = 20)	Protocol Sample 6: 24 Hours Post-ECMO (LDPV) (n = 4)
sRAGE	1,654.1 (929.9–2,753.6)	2,301.8 (1,035.2–3,168.6)	1,978.4 (800.2–4,362.2)	1,066.3 (679.6–4,645.3)	1,220.7 (836.1–7,298.3)	3,712.1 (1,907.6–4,432)
IL-6	338.2 (166–627.5)	348.6 (187.3–580.6)	587.8 (250–1,166.7)	520.8 (197.6–700.6)	388.2 (261.7–976.5)	1,939.5 (249.8–2,624.5)
IL-8	305.1 (187.4–396.6)	355.1 (204.3–510.3)	293.3 (170.9–436)	258 (149.3–406)	257.9 (133.5–450.4)	548.5 (319–560.6)
IL-10	30.3 (26.4–36.5)	24.7 (22.6–36.5)	28.5 (21.2–42.4)	29.7 (20.9–38.1)	30.2 (20.2–38.6)	28.8 (19.8–37.1)
CCL2	900.3 (814.8–1,711.5)	879.8 (778–1,224.1)	1,422.6 (711.3–2,077.7)	1,187.5 (809.5–2,403)	1,123.3 (654.6–2,031.4)	1,802.4 (1,207.6–2,421)
CCL5	7,574.8 (2,772.3–14,469.7)	6,561 (1,982–11,871.4)	2,825.1 (1,982.3–6,851.3)	2,112.9 (1,052.4–9,842.7)	2,499.2 (1,211.7–6,882.5)	4,204.5 (4,045.4–6,144.3)
CXCL9 ^{*§¶}	2,928.7 (1,590–5,108)	6,024.1 (4,066.3–9,537.5)	4,328.1 (1,967.7–6,384.7)	4,002.8 (1,803.5–6,322.3)	4,069.5 (1,796.1–5,392.8)	5,650.4 (3,114.5–6,036.8)
Ang-1	2,540.6 (1,320.5–4,898.8)	3,033.3 (694.7–4,238.8)	1,769.7 (982.7–4,300.1)	2,054.3 (1,161.6–2,712.3)	1,702.1 (450.6–2,506.9)	2,148.1 (1,515.9–2,998.6)
Ang-2	2,202.5 (1,448.2–2,756)	2,028.9 (1,412.7–2,850)	2,174.3 (1,523.6–3,240.1)	2,275 (1,533.6–3,386)	2,035.4 (1,472.9–2,691.5)	1,674.4 (1,114.1–2,041.3)
IP-10	1,811.8 (1,419–3,423.9)	2,121.7 (1,792.8–3,038.8)	2,764.3 (1,435.5–5,188.5)	2,892.4 (1,477.5–5,123.9)	2,817.1 (1,532.2–4,405.4)	1,415.9 (1,137.2–2,222.4)
IFN- α ^{*¶}	499.3 (378.6–616.8)	494.9 (337.5–674.3)	353.1 (235.2–719.5)	300.3 (199.5–519.6)	305.3 (169–631.7)	575 (563–624.2)
TNF- α	27.4 (21.6–37.2)	38 (30.4–54.9)	22.2 (14.6–71.2)	21.1 (9.1–30.2)	19.5 (7.3–45.5)	83.3 (58.2–102.2)
VEGF ^{*†}	98.5 (75.3–119.4)	42.5 (26.4–55.8)	72.1 (42.6–95.6)	53.9 (41.6–71.3)	54.8 (38–76.3)	50 (49.3–58.7)

NOTE. All values are median (IQR). Biomarker units in pg/mL.

Abbreviations: Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; CCL, chemokine ligand; CXCL9, chemokine ligand-9; IFN- α , interferon- α ; IL, interleukin; IP-10, interferon γ -inducible protein-10; LDPV, low-driving-pressure ventilation; LTVV, low-tidal-volume ventilation; sRAGE, soluble receptor for advanced glycation end-products; TNF- α , tumor necrosis factor α ; V-LDPV, very low driving-pressure ventilation; VEGF, vascular endothelial growth factor levels.

* $p \leq 0.05$ between protocol samples 1 and 2 (pre-ECMO with LTVV v post-ECMO with LTVV).

† $p \leq 0.05$ between protocol samples 3 and 4 (post-ECMO LDPV v V-LDPV). ‡ $p \leq 0.05$ between protocol samples 4 and 5 (post-ECMO V-LDPV v LDPV).

§ $p \leq 0.05$ between protocol samples 1 and 3 or 5 (pre-ECMO with LTVV v post-ECMO 16–24 hours).

¶ $p \leq 0.05$ between protocol samples 1 and 3 (pre-ECMO with LTVV v post-ECMO with LDPV) when associated with change in tidal volume.

¶ $p \leq 0.05$ between protocol samples 3 and 4 (post-ECMO LDPV v V-LDPV) when associated with change in tidal volume.

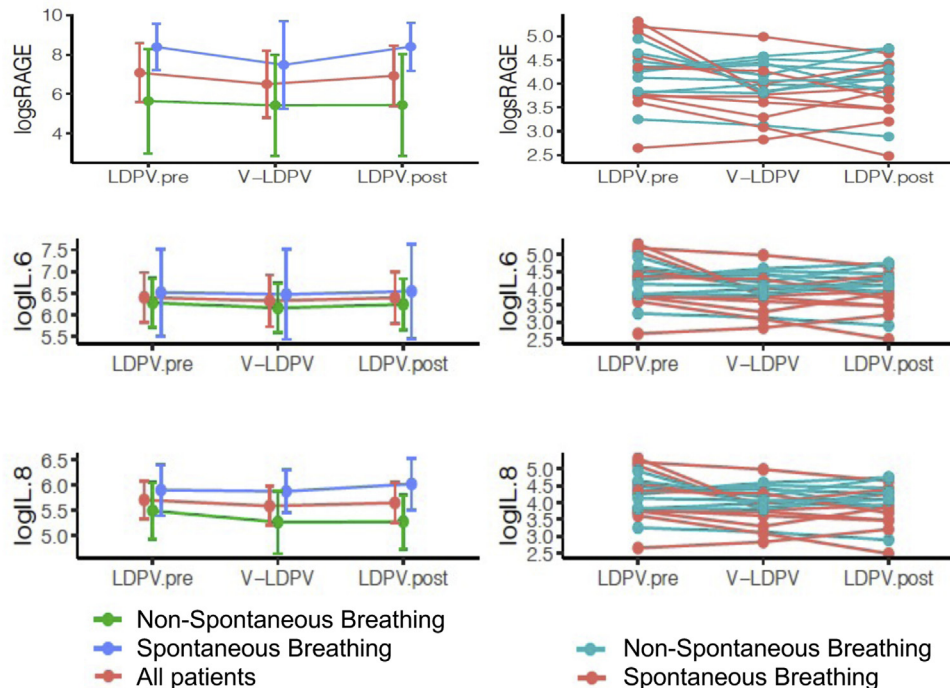


Fig 3. Biomarker changes during experimental ventilator protocol. Biomarker levels for all patients who underwent very low driving-pressure ventilation ($n = 21$). Left panels, average biomarker levels (with 95% CI) for soluble receptor for advanced glycation end-products, interleukin-6, and interleukin-8. Red for all patients, blue for spontaneously breathing patients, and green for patients with nonspontaneous breaths. Right panel, red for spontaneously ($n = 9$) and teal for non-spontaneous breathing ($n = 12$) patients. IL-6, interleukin 6; IL-8, interleukin 8; LDPV, low-driving-pressure ventilation; V-LDPV, very low driving-pressure ventilation; sRAGE, soluble receptor for advanced glycation end-products.

spontaneous respiratory efforts. Perhaps, as a result, there were no significant changes in the main biomarkers, IL-6, IL-8, and sRAGE. Even when controlling for spontaneous breathing and V_t change, the authors did not find consistent changes in plasma biomarkers in the first 24 hours post-ECMO.

This study demonstrated that V-LDPV and the sometimes-resulting apneic oxygenation were feasible and safe for the duration of the study period. Similar studies also reported no safety issues.^{15,16} However, there may be tradeoffs with V-LDPV and apneic oxygenation. All participants in the studies by Rozenchwajg et al. ($n = 16$) and Del Sorbo et al. ($n = 10$) were paralyzed using NMB, compared to only 19% of the participants in this study. Neuromuscular blockade and resulting sedation have associated risks, such as delirium, weakness, and ventilatory-associated pneumonia (VAP).^{28,29} One series of participants with COVID-19 requiring ECMO had VAP rates of 86%, similar to the authors' rate of 84%.³⁰ Although there are many possible explanations (eg, altered antimicrobial pharmacokinetics due to extracorporeal circuits, immunosuppression due to treatment with corticosteroids, and long duration of intubation), it is also possible that low V_t , atelectasis, and higher sedation requirements impair secretion clearance and therefore increase the risk of VAP.³¹⁻³⁴ Although speculative, there may be V_t (~2-4 mL/kg PBW) that is low enough to minimize VILI and/or biotrauma but high enough to avoid atelectasis, VAP, and require less sedation and/or NMB. This speculative V_t will likely need to be personalized to each patient.

A primary finding was that V-LDPV by itself did not reliably reduce V_t , even with deep sedation and normal serum pH

levels from ECMO support. Setting low ΔP in deeply sedated patients falsely may reassure clinicians that they are minimizing VILI and/or biotrauma; however, as the authors' study revealed, it may not consistently lower V_t if participants are spontaneously breathing (ie, higher transpulmonary pressure).³⁵ Mechanically ventilated patients may still have high respiratory drive (measured with $P_{0.1}$) despite deep sedation.³⁶ For patients with ARDS on ECMO, even high sweep gas rates do not reliably suppress respiratory drive, in contrast to those on ECMO for other indications.³⁷ Thus, although retrospective analysis has shown that lower ΔP may have a survival benefit for ARDS patients on ECMO, the authors caution that lower ΔP alone may not confer benefit.^{5,38} Although they recommend following the ELSO ECMO guidelines on ARDS ventilator settings, they do not discuss the use of NMB.³⁹ Patients who are spontaneously breathing or have increased work of breathing during LDPV, with resulting harmful or unwanted V_t a may require increasing sedation (if it successfully lowers respiratory drive) and/or NMB to minimize transpulmonary pressure (TPP). In short, TPP is likely more reflective of VILI and/or biotrauma than ΔP or mechanical power.

The study authors found no significant change in plasma biomarkers of lung injury and inflammation among the 3 studied ventilator strategies (LTVV, LDPV, and V-LDPV), possibly because they did not reliably change V_t . Even when investigating changes in V_t (rather than ventilator ΔP) with changes in biomarkers, contrary to the authors' hypothesis, they did not see a reliable correlation. These results were similar to Rozenchwajg et al. who observed no difference between

different combinations of ΔP and PEEP, some of which should be more protective (eg, high PEEP and low ΔP) in their cohort of 16 ECMO participants.¹⁶ For example, in their study, IL-6 and sRAGE were unchanged 12 hours post-ventilator changes. However, prior to their ventilator interventions, biomarkers (IL-6 and sRAGE) decreased after 24 hours of protective ventilation (pplat <24) while on ECMO, compared to pre-ECMO baseline. The decrease in biomarkers compared to pre-ECMO could reflect NMB (as all 16 patients were paralyzed) and/or changes over time. It should be noted that the Rozenwajg et al. and Del Sorbo et al. studies were performed prior to the COVID-19 pandemic. Recently, in 22 patients with ARDS due to COVID-19, Lebreton et al. similarly found that IL-6 levels decreased on ECMO over 48 hours.⁴⁰ Consistent with these prior reports and in contrast to older literature, the authors herein did not find a significant increase in biomarkers with ECMO initiation in their participants.¹⁷ Compared to older ECMO circuits, current circuits are smaller and more biocompatible, possibly decreasing the effects on systemic inflammation and biomarkers.⁴¹

The authors' results differed from Del Sorbo et al., who also tested apneic oxygenation in 10 participants in crossover fashion; from standard ELSO-recommended LDPV to no ΔP (ie, only PEEP) to increased ΔP ($\Delta P = 20$ cmH₂O) for 2 hours at each setting.¹⁵ All patients were paralyzed, and the range of V_t during the experiment was about 4 mL/kg. With this change in V_t , there were small, though statistically significant changes in some biomarkers, notably IL-6. There are several possible explanations. First, the V_t does impact biomarker profile, but the authors' study and Rozenwajg did not have large enough changes in V_t or ΔP (ie, TPP).¹⁶ Second, the authors' patients with COVID-19 ARDS might have had more lung injury than ARDS from other etiologies, and the changes in biomarkers with changes in ventilation strategy might have been difficult to detect. For example, some IL-6 levels reported by Lebreton et al. were 5- to 10-fold higher (similar to this study) than in the Del Sorbo et al. study. Third, the authors studied their participants in the first 24 hours post-ECMO, although both the protocols of Del Sorbo et al. and Rozenwajg et al. started 24-to-48 hours post-ECMO. Thus, it is possible that the decrease in biomarkers could have been time-dependent. Finally, most of the authors' patients were not on NMB, which might have additional antiinflammatory effects.⁴²

This study had a few limitations, primarily as a single-center study with a modest sample size. However, the authors' sample size was larger than in recent studies.^{15,16} They did not routinely investigate cardiac function, which may be important. As previously noted, patients with known cardiac dysfunction were not offered ECMO due to resource limitations from the ongoing COVID-19 pandemic. The authors' population exclusively had ARDS due to COVID-19, whereas many other ECMO and ARDS studies had different etiologies of lung injury. However, due to the severe lung injury in COVID-19 ARDS, the authors' findings may not be generalizable to other etiologies of ARDS. Furthermore, to minimize confounding factors, their protocol did not alter PEEP or the respiratory rate, both of which may have biomarker implications. The

TPP was measured only at one time during the authors' protocol; had it been measured continuously across all time points, the study could have assessed the association between lung stretch and biomarker concentration, which is more biologically relevant. As a physiologic study, the authors were not powered to detect clinical outcomes such as mortality. Finally, the study intervention was relatively brief by design (although biomarkers have been shown to have significant changes as quickly as 1-hour postventilator changes), as a longer duration of intervention may have further increased difficulty in data interpretation in the setting of the vicissitudes of critical illness.¹⁴

Conclusions

V-LDPV is feasible and safe for patients on ECMO for ARDS. However, V_t was not uniformly reduced by ΔP adjustments alone due to spontaneous respiratory efforts. The study authors did not find that changes in ΔP or V_t correlated with ARDS biomarker levels within the relatively modest (but typical) V_t studied. Their results suggested that, for patients on ECMO, additional sedation (if effective) and/or NMB might be needed to maintain low V_t that is considered protective. Future studies are needed to evaluate if there is a protective effect of NMB in patients with severe ARDS who require VV-ECMO and persist with large V_t despite deep sedation and low ΔP . Further studies with clinical outcomes of early V-LDPV are also needed.

Acknowledgments

The authors gratefully acknowledge the family members who agreed to permit patient participation, and their perfusionists, nurses, respiratory therapists, nurse practitioners, and physicians who care for their patients at UC San Diego Health. The authors acknowledge Robert Abbott, PhD supported by National Institutes of Health (grant #K99AI145762), and Shane Crotty, PhD supported by Cooperative Centers for Human Immunology (grant #AI142742) from the La Jolla Institute of Immunology for help with biomarker measurement.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.11.033.

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