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ORIGINAL RESEARCH PAPER

Modifiable Mechanical Ventilation Targets Are Associated With Improved Survival in Ventilated VA-ECLS Patients

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ABSTRACT

BACKGROUND In acute respiratory distress syndrome (ARDS), lung protective ventilation (LPV) improves patient outcomes by minimizing ventilator-induced lung injury. The value of LPV in ventilated patients with cardiogenic shock (CS) requiring venoarterial extracorporeal life support (VA-ECLS) is not known, but the extracorporeal circuit provides a unique opportunity to modify ventilatory parameters to improve outcomes.

OBJECTIVES The authors hypothesized that CS patients on VA-ECLS who require mechanical ventilation (MV) may benefit from low intrapulmonary pressure ventilation (LPPV), which has the same end goals as LPV.

METHODS The authors queried the ELSO (Extracorporeal Life Support Organization) registry for hospital admissions between 2009 and 2019 for CS patients on VA-ECLS and MV. They defined LPPV as peak inspiratory pressure at 24 hours on ECLS of $<$ 30 cm H_2O. Positive end-expiration pressure and dynamic driving pressure DDP) at 24 hours were also studied as continuous variables. Their primary outcome was survival to discharge. Multivariable analyses were performed that adjusted for baseline Survival After Venoarterial Extracorporeal Membrane Oxygenation score, chronic lung conditions, and center extracorporeal membrane oxygenation volume.

RESULTS A total of 2,226 CS patients on VA-ECLS were included: 1,904 received LPPV. The primary outcome was higher in the LPPV group vs the no-LPPV group (47.4% vs 32.6%; $P < 0.001$). Median peak inspiratory pressure (22 vs 24 cm H_2O; $P < 0.001$) as well as DDP (14.5 vs 16 cm H_2O; $P < 0.001$) were also significantly lower in those surviving to discharge. The adjusted OR for the primary outcome with LPPV was 1.69 (95% CI: 1.21-2.37; $P = 0.0021$).

CONCLUSIONS LPPV is associated with improved outcomes in CS patients on VA-ECLS requiring MV.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ARDS = acute respiratory distress syndrome

CS = cardiogenic shock

DDP = dynamic driving pressure

ECMO = extracorporeal membrane oxygenation

LPV = lung protective ventilation

LPPV = low intrapulmonary pressure ventilation

LVEDP = left ventricular end diastolic pressure

PEEP = positive end-expiratory pressure

PIP = peak inspiratory pressure

$P_{plateau}$ = plateau inspiratory pressure

PPV = positive pressure ventilation

VA-ECLS = venoarterial extracorporeal life support

VILI = ventilator-induced lung injury

Cardiogenic shock (CS) accounts for approximately 15% to 20% of admissions to cardiovascular intensive care units[1,2] and portends a poor prognosis with an estimated in-hospital mortality of 30% to 40%, which has changed little over the last 3 decades.[1-3] Respiratory failure requiring positive pressure ventilation (PPV), either noninvasively via a mask interface or invasively through endotracheal intubation, is common among CS patients, with an estimated incidence of 50% to 88%.[1]

General recommendations for ventilator management in CS patients have frequently been extrapolated from prior acute respiratory distress syndrome (ARDS) studies. One such ventilation strategy is lung protective ventilation (LPV), which refers to low tidal volume ventilation aimed at reducing intrapulmonary pressures with the goal of preventing excessive airway distension and resultant barotrauma.[4] LPV has been shown to improve outcomes including mortality in patients with respiratory failure caused by noncardiac ARDS.[4,5] In the landmark ARDS Network trial, low tidal volume ventilation (6 mL/kg predicted body weight targeting a plateau inspiratory pressure [$P_{plateau}$] of <30 cm H_2O) resulted in significantly reduced in-hospital mortality, ventilator-free days, and nonpulmonary organ failure compared to traditional tidal volume ventilation (12 mL/kg predicted body weight targeting a $P_{plateau}$ of <50 cm H_2O).[4] We hypothesized that LPV might improve lung as well as cardiac function in ventilated patients with CS. The ELSO (Extracorporeal Life Support Organization) registry is a large international registry of patients with CS that collects selected ventilatory parameters but does not collect tidal volume, which is the major criterion used in defining LPV. However, the intention of a low tidal volume is to have lower intrapulmonary pressures, assessed by plateau pressure and driving pressure (DP). Thus, we used available parameters (peak inspiratory pressure [PIP] and dynamic DP [DDP]) that are collected in the ELSO registry as a first evaluation of the effect of low intrapulmonary pressure ventilation (LPPV) on cardiac function in CS. Although the benefit of LPPV that reduces barotrauma is well established in ARDS patients and those requiring veno-veno extracorporeal life support,[5] its impact on CS patients requiring venoarterial extracorporeal life support (VA-ECLS) with concomitant respiratory failure is largely unstudied. There remains a paucity of published reports on how modifiable ventilatory parameters, such as positive end-expiratory pressure (PEEP), PIP, and dynamic transpulmonary DP (a direct measure of mechanical stress applied to the lungs), affect outcomes in CS patients on VA-ECLS, especially if deployed early in the disease process. In patients without ECLS, the ability to modify these parameters may be limited by acid-base disturbances and hemodynamic compromise from low cardiac output and hypotension. These problems are minimized in VA-ECLS because gas exchange occurs independently of the ventilator circuit. Thus, there is growing interest in ventilatory strategies to improve outcomes for patients on ECLS.[6] Some strategies include "ultraprotective" mechanical ventilation to provide lung rest while on ECLS.[6-9] It is possible that in addition to improving pulmonary outcomes, such ventilatory strategies may also lead to improved cardiac outcomes, especially through unique interactions with cardiac hemodynamics. Furthermore, PEEP may have a role to play in promoting reverse myocardial remodeling by reducing left ventricular (LV) transmural pressure.[10]

We analyzed associations between such modifiable ventilatory parameters, intrapulmonary pressures, and survival to discharge after VA-ECLS support to determine potential benefits of LPPV and higher PEEP in patients with CS on VA-ECLS requiring mechanical ventilation.

METHODS

A retrospective review was performed of adult patients (age >18 years) in the ELSO registry who received VA-ECLS and mechanical ventilation for CS between 2009 and 2019. Our study was approved by the Vanderbilt University Medical Center Institutional Review Board and the ELSO Scientific Oversight Committee. The ELSO registry is a large international database of patients who have received ECLS, with member centers from more than 50 countries around the world.[11] The year 2019 was chosen as the cutoff for analysis to exclude confounding caused by the COVID-19 pandemic. Patients were excluded from our analysis if they had congenital heart disease, experienced pre-ECLS cardiac arrest, or had a durable mechanical circulatory support device at the time of extracorporeal membrane oxygenation (ECMO) initiation, and only the first ECLS run was included for each patient.

Because the ELSO registry does not capture plateau pressures or tidal volume, we used PIP at 24 hours post-ECLS initiation as our primary measure of LPPV. PIP was used for our analysis because it has been

shown to correlate well with plateau pressure in prior studies.[4] Similarly, DDP at 24 hours post-ECLS initiation was used as a surrogate for DP and was calculated as the difference between PIP and PEEP. Prior studies have established DDP as an acceptable alternative to DP.[12]

Our primary outcome was index hospitalization survival to discharge. The overall cohort was analyzed using 2 different categorizations: survivors to discharge vs nonsurvivors and those receiving LPPV (PIP of ≤30 cm H_2O) vs non-LPPV (PIP of >30 cm H_2O). Baseline characteristics including Survival After Venoarterial ECMO (SAVE) score were obtained for each of these groups. The SAVE score is a multivariable predictor of survival for patients on VA-ECLS developed using the ELSO registry and accounts for factors such as etiology of CS, age, weight, renal dysfunction, liver failure, pulse pressure, and duration of intubation before ECLS.[13] Each of the 2 groups was compared using the Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables. Continuous variables are presented as median and IQR, and categorical variables are presented as frequency and percentage.

PIP, DDP, and PEEP were analyzed as continuous variables to test their association with survival to discharge. Logistic regression models were used to assess the effect of variables of interest (PIP <30 cm H_2O, PIP, DDP, and PEEP) on mortality, adjusted for SAVE score, chronic lung conditions, and volume of the ECMO center. Restricted cubic spline was initially applied on continuous variables and was removed on the final model if not significant. Predicted plot was generated to present the relationship of nonlinear predictors and outcomes.

TABLE 1 Baseline Characteristics: PIP

	PIP >30 cm H_2O (n = 322)	PIP ≤30 cm H_2O (n = 1,904)	*P* Value
Age, y, median	58.1 (47.4-65.7)	59.2 (47.6-67.7)	0.086
Male	58.8	65.8	0.015
BMI, kg/m^2, median	31.14 (26.38-36.71)	28.28 (24.27-32.37)	<0.001
Race			0.507
White	59.9	60.1	
Black	14.9	12.8	
Other	25.2	27.1	
Ventilation type			0.549
Conventional[a]	99.7	99.8	
Other	0.3	0.2	
Etiology of cardiogenic shock			
Myocarditis	1 (0.3)	17 (0.9)	0.281
Refractory VT/VF	1 (0.3)	8 (0.4)	0.774
Postheart or postlung transplant	4 (1.2)	21 (1.1)	0.826
Congenital heart disease	0 (0)	0 (0)	0.00
Other (including ADHF and AMI)	316 (98)	1,858 (98)	0.525
Patients from ECMO centers by volume			0.818
Small volume	3.4	4.1	
Average volume	17.1	17.3	
Large volume	79.5	78.6	
SAVE score	-2.77 ± 3.77	-1.76 ± 3.91	0.002
SAVE score	-2.0 (-6.0 to 0)	-2.0 (-5.0 to 1.0)	0.002
Pump flow, L/min	4.15 (3.63-4.77)	4.12 (3.55-4.8)	0.595
ECMO run, h	120 (68-209)	131 (74-207)	0.147
P_{CO_2}	38 (34-42)	38 (34-42)	0.515
P_{O_2}	186 (108-314.5)	150 (99-254)	<0.001
pH	7.41 (7.36-7.47)	7.42 (7.38-7.47)	0.072
PEEP	10 (5-10)	8 (5-10)	<0.001
Left ventricular venting	83 (25.7)	455 (23.9)	0.543
Pre-existing chronic lung conditions	5 (1.6)	21 (1.1)	0.487
Survival to discharge	105 (32.6)	902 (47.4)	<0.001

Values are %, n (%), mean ± SD, or median (IQR), unless noted otherwise. [a]Conventional mechanical ventilation includes pressure control, pressure regulated volume control, volume control, and inverse ratio ventilation.

ADHF = acute decompensated heart failure; AMI = acute myocardial infarction; BMI = body mass index; ECMO = extracorporeal membrane oxygenation; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; SAVE = Survival After Venoarterial Extracorporeal Membrane Oxygenation; VF = ventricular fibrillation; VT = ventricular tachycardia.

RESULTS

Of the 2,226 CS patients on VA-ECLS analyzed, 1,904 patients met our criteria for LPPV, and 322 did not. Baseline characteristics, ECLS and ventilator parameters, and blood gas data are reported by PIP status in **Table 1**. The PIP <30 cm H_2O group had a higher proportion of male patients (65.8% vs 58.8%; $P = 0.015$), lower median body mass index (28.3 vs 31.1 kg/m^2; $P < 0.001$), and lower mean SAVE score (-1.76 ± 3.91 vs -2.77 ± 3.77; $P = 0.002$). They had lower P_{O_2} (150 vs 186 mm Hg; $P < 0.001$) and were receiving lower PEEP (8 vs 10 cm H_2O) at 24 hours. There was no difference in rates of pre-existing chronic lung disease (1.1% vs 1.6%; $P = 0.487$). Patients who received lower intrapulmonary pressure ventilation were more likely to survive the index hospitalization (47.4% vs 32.6%; $P < 0.001$). This relationship remained true even when adjusted for baseline SAVE score, chronic lung conditions, and center ECMO volume (adjusted OR: 1.69 [95% CI: 1.21-2.37]; $P = 0.0021$) (**Table 2** and **Central Illustration**).

Supplemental Table 1 compares the baseline characteristics of patients who survived to discharge to those who died during the index hospitalization. Of the 2,226 patients analyzed, 1,007 (45%) survived to hospital discharge, and 1,219 did not. Patients surviving to discharge were younger (55.8 vs 61.4 years; $P < 0.001$), had lower body mass index (28.25 vs 28.72 kg/m^2; $P = 0.03$), and had more favorable SAVE scores (-0.82 ± 3.85 vs -2.78 ± 3.72; $P < 0.001$). At

TABLE 2 Modifiable Ventilation Variables Associated With Survival

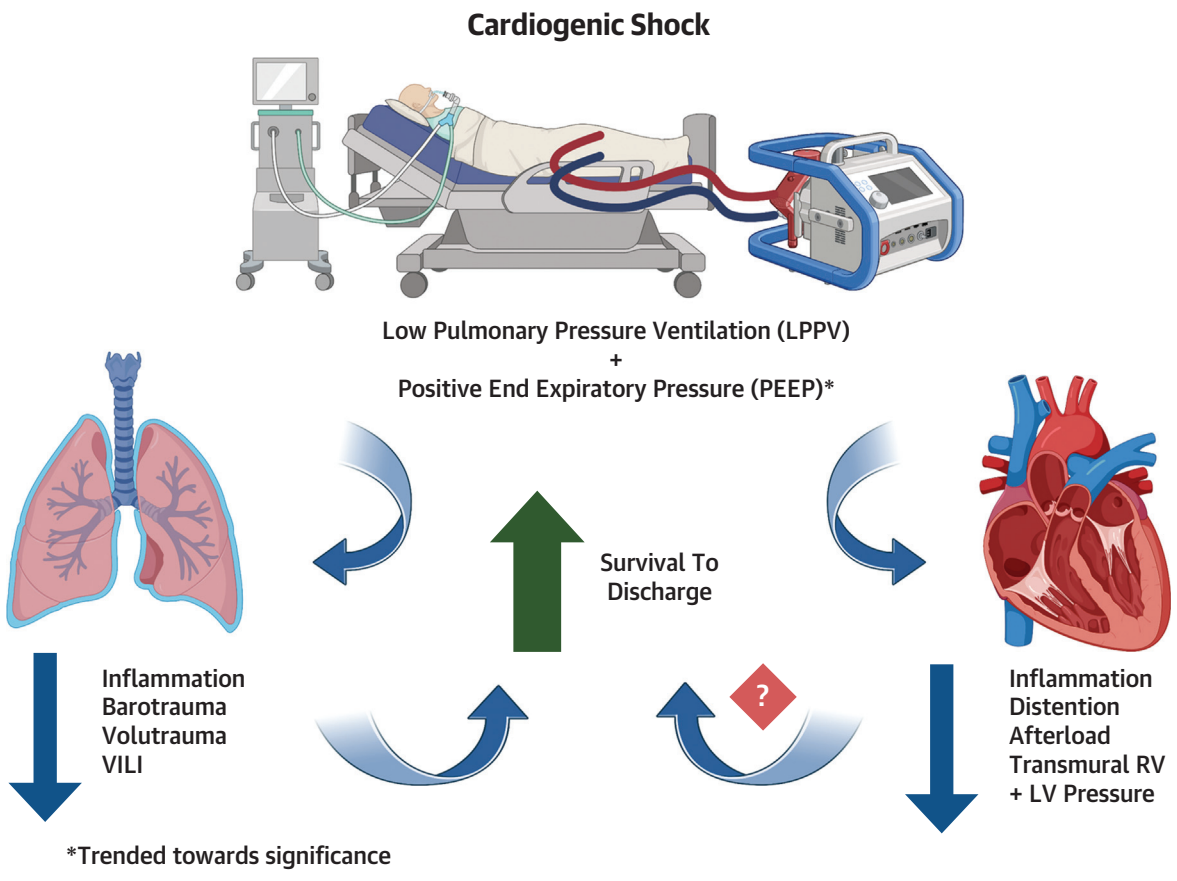
	aOR Adjusted for SAVE Score	*P* Value	aOR Adjusted for SAVE Score, Chronic Lung Conditions, and Volume of ECMO Center	*P* Value
PIP <30 cm H_2O	1.68 (1.20-2.36)	0.0023	1.69 (1.21-2.37)	0.0021
Continuous PIP	0.87 (0.78-0.977)	0.018	0.87 (0.78-0.976)	0.018
Continuous DDP	0.84 (0.75-0.945)	0.0033	0.84(0.75-0.944)	0.0032
Continuous PEEP	1.08 (0.97-1.20)	0.14	1.08 (0.975-1.20)	0.14

Values are HR (95% CI), unless otherwise indicated.
aOR = adjusted OR; DDP = dynamic driving pressure; other abbreviations as in Table 1.

24 hours after ECLS initiation, the survival group had significantly lower median PIP (22 vs 24 cm H_2O; $P < 0.001$), DDP (14.5 vs 16 cm H_2O; $P < 0.001$), and Po_2 (135.9 vs 171; $P < 0.001$). Average mean airway pressure at 24 hours was also lower in the survival group (11 vs 12 cm H_2O) but did not meet statistical significance ($P = 0.06$).

Multivariable regression models of PIP at 24 hours, adjusted for SAVE score alone (Figure 1A) and for SAVE score, underlying chronic lung disease, and center ECMO volume (Figure 1B) demonstrated a nonlinear relationship with survival probability. DDP was significantly associated with survival to discharge in multivariable models including SAVE score alone (Figure 2A) and SAVE score, underlying chronic lung disease, and ECMO center volume (Figure 2B) (adjusted OR: 0.842 [95% CI: 0.75-0.944]; $P = 0.0032$). Higher PEEP was associated with improved survival but was not statistically significant (Figure 3A) ($P = 0.14$) (Figure 3B) ($P = 0.14$).

CENTRAL ILLUSTRATION Benefits of Low Pulmonary Pressure Ventilation and Positive End-Expiratory Pressure in Cardiogenic Shock Patients on VA-ECLS and Mechanical Ventilation



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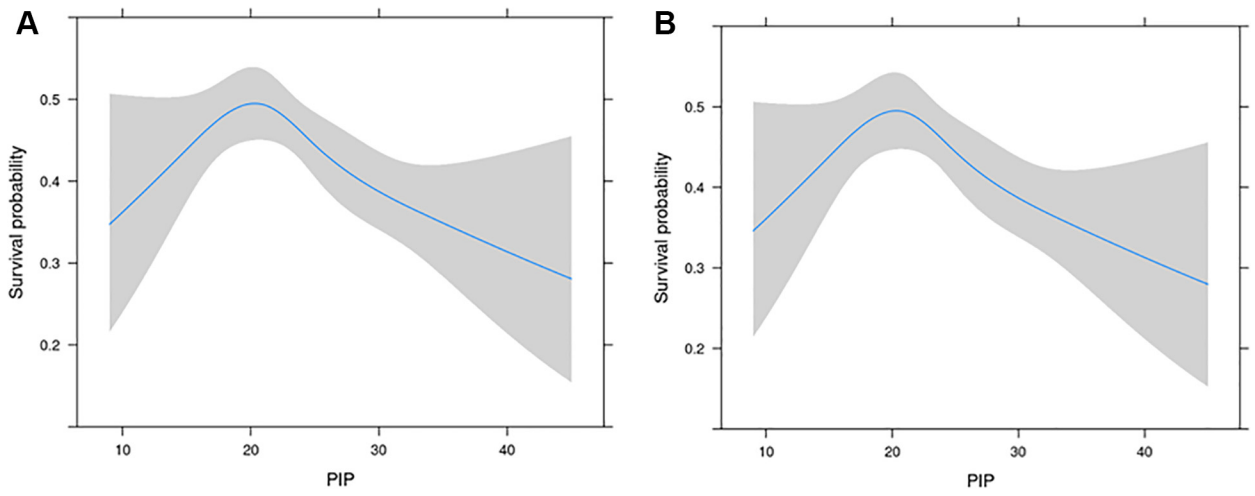
Created using www.biorender.com. LV = left ventricular; RV = right ventricular; VA-ECLS = venoarterial extracorporeal life support; VILI = ventilator-induced lung injury.

FIGURE 1 **Association of Peak Inspiratory Pressure at 24 Hours and Survival**

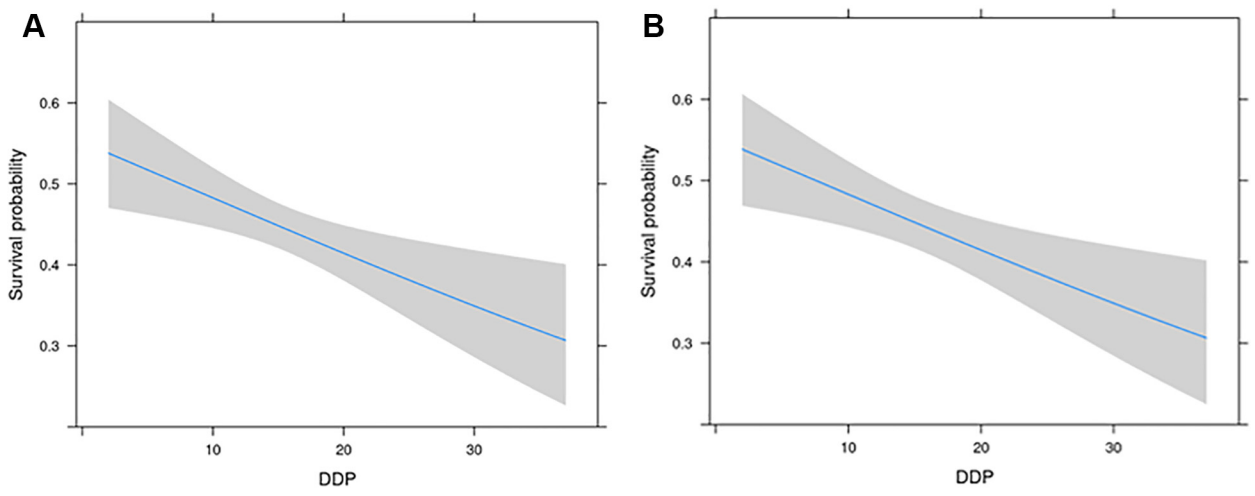


(A) PIP at 24 hours as associated with survivability (adjusted for SAVE score). **(B)** PIP at 24 hours as associated with survivability (adjusted for SAVE score, chronic lung conditions, and volume of ECMO center). ECMO = extracorporeal membrane oxygenation; PIP = peak inspiratory pressure; SAVE = Survival After Venoarterial Extracorporeal Membrane Oxygenation.

DISCUSSION

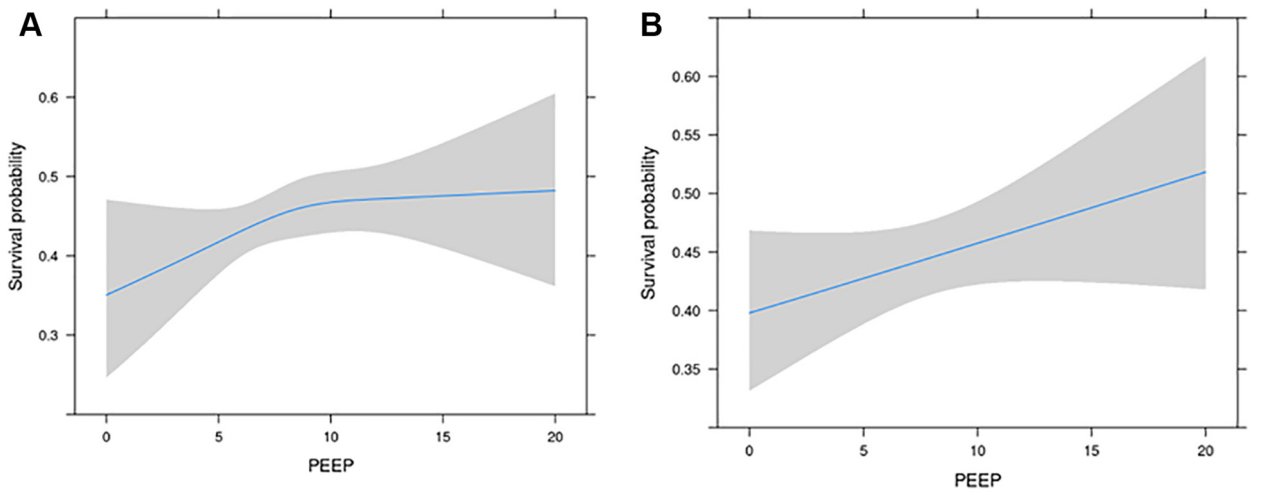
In this study of mechanically ventilated CS patients on ECLS, we show, for the first time to our knowledge, that LPPV, as assessed by PIP at 24 hours, was associated with improved survival to discharge. Increase in lung stress with each ventilator breath as measured by DDP at 24 hours was associated with increased mortality during the index hospitalization. We also found a trend for survival to be better in those patients receiving higher PEEP, although it did not reach statistical significance.

FIGURE 2 **Association of Driving Pressure at 24 Hours and Survival**



(A) Driving pressure at 24 hours as associated with survivability (adjusted for SAVE score). **(B)** Driving pressure at 24 hours as associated with survivability (adjusted for SAVE score, chronic lung conditions, and volume of ECMO center). DDP = dynamic driving pressure; other abbreviations as in Figure 1.

FIGURE 3 Association of Peak End-Expiratory Pressure at 24 Hours and Survival



(A) PEEP at 24 hours as associated with survivability (adjusted for SAVE score). **(B)** PEEP at 24 hours as associated with survivability (adjusted for SAVE score, chronic lung conditions, and volume of ECMO center. PEEP = positive end-expiratory pressure; other abbreviations as in Figure 1.

The parameters we used to define LPPV are not the same as for LPV but are likely to be associated with many of the same benefits as LPV. In ARDS, LPV improves patient outcomes by minimizing the risk of ventilator-induced lung injury (VILI). The underlying mechanisms of VILI are believed to be multiple, including alveolar overdistension ("volutrauma"), increased intrapulmonary pressure ("barotrauma"), repeated opening and closing of small airways related to alveolar collapse ("atelectrauma"), and secondary inflammation related to these mechanical injuries ("biotrauma"), and it is likely that many of these same mechanisms are operative with LPPV.[14]

There are several plausible pulmonary and extrapulmonary mechanisms by which lower PIPs may improve survival in CS patients. First, direct pulmonary benefit of lower intrapulmonary pressure includes promoting lung recovery in acute lung injury by minimizing the risk of VILI. In the landmark ARDS Network Trial, the initial Pa_{O_2}:Fi_{O_2} ratio in the cohort receiving ventilation targeting lower intrapulmonary pressures was worse when compared to the traditional ventilation group, but it improved over time in response to LPV, whereas the traditional ventilation group worsened.[4] Additional findings from the same ARDS Network trial draw attention to potential extrapulmonary benefits of LPV. In the trial, LPV was associated with significantly decreased plasma interleukin 6 values when compared to traditional ventilation.[4] This may reflect a decrease in both lung and systemic inflammatory responses to acute lung injury. Lower systemic inflammation indeed led to a higher number of days without organ or system failure in the LPV cohort compared to those receiving traditional ventilation.[4,15] In CS patients treated with VA-ECLS, respiratory failure is a rare (<5%) cause of death.[16,17] Hence, the "cardioprotective" benefit of LPPV in our study cohort is likely to not be completely attributable to improvement in lung function only. In our study, the improved survival is an absolute benefit of nearly 15%, suggesting that cardiac outcomes may have also been improved. Of note, the benefit of targeting lower intrapulmonary pressures has previously been shown to be independent of baseline lung compliance, suggesting that this strategy is advantageous regardless of lung compliance.[4] Although poor lung compliance may limit the ability to deploy this strategy while maintaining adequate gas exchange, this limitation is overcome by the presence of extracorporeal gas exchange in our cohort.

In addition to low tidal volume ventilation, there is a growing interest in titrating other ventilatory parameters, such as DP and PEEP, to help improve survival in mechanically ventilated patients with ARDS. DP is defined as the difference between plateau pressure and PEEP and reflects the mechanical stress that the lung experiences with each breath. It represents tidal volume adjusted for respiratory system compliance.[18] Recent analyses have demonstrated

that DP is the variable that is most strongly associated with mortality in ARDS patients.[18-22] In our study, lower DDP at 24 hours on ECLS was consistently associated with increased survival to discharge. Lower DDP may be associated with lower mortality because it results in lower cyclic lung stretch during mechanical ventilation.[12] There is a strong correlation between cyclic stretch, VILI, DDP, and survival in patients with ARDS.[20] DP represents stress applied to the lungs, and hence, adjusting tidal volume according to DP rather than predicted body weight may render improved outcomes, especially among patients with severe lung injury and poor lung compliance.[23] An additional advantage of DDP is that it can be used to maximize PEEP to help with lung recruitment while ensuring a more homogenous distribution of stress and strain across the lung parenchyma.

In our cohort of CS patients, we found a trend toward improved survival to discharge with increasing PEEP. Although this trend did not reach statistical significance, given PEEP's diverse effects on cardiac hemodynamics, it warrants a brief discussion as a potential therapeutic target to promote myocardial recovery. PEEP decreases venous return and subsequently leads to decreased right ventricular (RV) and LV preload.[1,24] Additionally, PEEP increases RV afterload while decreasing LV afterload.[1,24] Increased aortic pressure in the setting of PPV leads to baroreceptor activation, reflex vasodilation, and reduction in systemic vascular resistance, which in turn lowers LV afterload. A decreased LV preload and afterload ultimately leads to reduction in LV distension, which is associated with decreased wall stress and lower myocardial oxygen demands. By definition, $\Delta LVEDP_{intracavitary} = \Delta LVEDP_{transmural} + \Delta$ external pressures, and hence, increased external pressure and reduced LV volume with PEEP will result in reduced transmural left ventricular end diastolic pressure (LVEDP) or myocardial "wall stress."[10] Thus, PEEP offers an opportunity for improved myocardial mechanics, which may be beneficial in patients with CS.[10] Overall, the effects of PEEP can be helpful for patients with impaired LV systolic function by optimizing preload, decreasing afterload, and increasing cardiac output. One challenge to providing high PEEP in CS patients is the resultant hypotension, especially in preload-dependent states including RV dysfunction, pericardial tamponade, and pericardial constriction.[1] Because the extracorporeal circuit provides required circulatory support, patients supported on VA-ECLS are uniquely situated to benefit from higher PEEP.

Our findings suggest that lower intrapulmonary pressure ventilation, targeting lower PIP and DDP as early as 24 hours post-ECLS initiation, may be beneficial in patients in CS on VA-ECLS. In addition to being lung protective, this strategy may also be cardioprotective. Similar to our findings, Tonna et al[25] recently showed improved survival with lower PIP and DDP at 24 hours in ECMO cardiopulmonary resuscitation patients. The guiding principles of LPPV as defined in our cohort and conventional LPV are similar because they both aim to minimize the risk of VILI caused by barotrauma. Our findings would advocate for future prospective trials where lower tidal volumes and plateau pressures (the conventional definition of LPV) are systematically studied as therapeutic targets in the treatment of CS.

STUDY LIMITATIONS. In addition to this being a retrospective analysis, our results should be interpreted with several limitations in mind. First, the ELSO database does not capture tidal volumes or plateau pressures in patients receiving mechanical ventilation. Hence, we used PIP in defining LPPV. The ARDS Network study has previously shown that PIP trends similarly to plateau pressure.[4] Similarly, the ELSO database also does not provide further categorization of the ventilator mode than reported in our analysis. Second, changes in ventilator settings and pulmonary pressures beyond the first 24 hours on ECLS are not captured by the ELSO database. Lack of data showing the entire ventilatory course may in part explain the paradoxical association of very low PIP and worse survival in our cohort. An alternate plausible explanation is that very low PIP reflects underinflated lungs with small tidal volumes delivered during "lung-rest" ventilation while on VA-ECLS. This would result in both worsening atelectatic trauma and higher pulmonary vascular resistance and RV strain.[1] Furthermore, very low PIP could have resulted from patient-ventilator dyssynchrony and flow starvation, which would also adversely affect survival. We would expect more granular data to further improve outcome discrimination. Third, it is possible that higher airway pressures may reflect less compliant lungs rather than desired ventilatory settings. However, because patients on VA-ECLS can oxygenate and ventilate through the extracorporeal membrane, our study does raise the question of whether the ventilator setting should be actively titrated to target lower airway pressures. Fourth, a complete set of invasive cardiac hemodynamics is unavailable in the ELSO registry to definitively establish RV and LV pressures

and function while on ECLS support. Furthermore, the exact etiology of CS in those patients with International Classification of Diseases-9th Revision or -10th Revision codes for both acute myocardial infarction and acute decompensated heart failure is hard to delineate, given the limitations of the ELSO database. Finally, we cannot show causality in this observational analysis, and hence, our findings should be considered hypothesis generating. We cannot exclude residual confounding.

CONCLUSIONS

Lower airway pressures are associated with improved outcomes in CS shock patients on VA-ECLS requiring mechanical ventilation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Lower intrapulmonary pressure ventilation is associated with improved outcomes in mechanically ventilated CS patients on VA-ECLS. Mechanisms of benefit probably include direct cardiac benefit in addition to pulmonary benefit. Higher PEEP in patients who can tolerate it may be a therapeutic target to facilitate myocardial recovery.

TRANSLATIONAL OUTLOOK: Precise mechanisms by which LPPV renders its cardiac-specific benefits remain unknown and will need to be the focus of future studies.

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APPENDIX For a supplemental table, please see the online version of this paper.