CONCISE CLINICAL REVIEW

Mechanical Ventilation for Acute Respiratory Distress Syndrome during Extracorporeal Life Support

Research and Practice

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Abstract

Ventilator-induced lung injury remains a key contributor to the morbidity and mortality of acute respiratory distress syndrome (ARDS). Efforts to minimize this injury are typically limited by the need to preserve adequate gas exchange. In the most severe forms of the syndrome, extracorporeal life support is increasingly being deployed for severe hypoxemia or hypercapnic acidosis refractory to conventional ventilator management strategies. Data from a recent randomized controlled trial, a *post hoc* analysis of that trial, a meta-analysis, and a large international multicenter observational study suggest that extracorporeal life support, when combined with lower V_T and airway pressures than the current standard of care, may improve outcomes compared with conventional management in patients with the most severe forms of ARDS. These findings raise important questions not only about the optimal ventilation strategies for patients receiving extracorporeal support but also regarding how various mechanisms of lung injury in ARDS may potentially be mitigated by ultra–lung-protective ventilation strategies when gas exchange is sufficiently managed with the extracorporeal circuit. Additional studies are needed to more precisely delineate the best strategies for optimizing invasive mechanical ventilation in this patient population.

Keywords: acute respiratory distress syndrome; extracorporeal life support; extracorporeal membrane oxygenation; extracorporeal carbon dioxide removal; ventilator-induced lung injury

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Key Points

- Ventilator-induced lung injury is a major contributor to morbidity and mortality in acute respiratory distress syndrome (ARDS), driven in large part by injurious mechanical forces.
- Extracorporeal life support (ECLS) can supplement or supplant native lung gas exchange in ARDS, allowing reductions in the mechanical forces contributing to ventilator-induced lung injury.
- Conventional management strategies (standard-of-care lung-protective ventilation, prone positioning, positive end-expiratory pressure titration, conservative fluid balance, and perhaps neuromuscular blockade) should be optimized before consideration of ECLS.
- The ventilation strategies employed in the EOLIA (Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome) trial are a reasonable default standard of care for invasive mechanical ventilation in patients with ARDS receiving extracorporeal membrane oxygenation, although we suggest targeting respiratory rates of 10 (the lower range in EOLIA) or less.
- Excess work of breathing may promote lung injury in ARDS and should be avoided, regardless of whether ECLS is used.
- More data are needed to determine the ventilator parameters that are associated with improved short- and long-term outcomes.

Extracorporeal life support (ECLS) can support gas exchange in patients with the acute respiratory distress syndrome (ARDS) whose oxygenation or ventilation cannot be maintained adequately with best practice conventional mechanical ventilation and adjunctive therapies, including prone positioning (1). ECLS enables the use of lower V_T and airway pressure in patients whose gas exchange could otherwise be maintained only at the expense of injurious mechanical ventilation strategies (1–3). Ventilator-induced lung injury (VILI) is a key contributor to morbidity and mortality in ARDS (4), particularly among those considered for ECLS. Therefore, adopting a lung-protective ventilation strategy beyond the current standard of care concomitantly with the application of ECLS in these patients appears to be key to realizing the potential benefit of this strategy. The objectives of this review are to summarize the current understanding of the role ECLS may play in minimizing VILI; suggest best practice mechanical ventilation strategies during ECLS, given the existing data; describe the interplay between ECLS, gas exchange, and ventilator parameters; and identify the areas of research that are needed to better inform the optimal management of mechanical ventilation and spontaneous breathing efforts during ECLS. The suggestions put forth in this narrative review reflect consensus expert opinions of clinicians and researchers with expertise in mechanical ventilation, ARDS, and ECLS that originated from a roundtable discussion at the Fourth Annual International ECMO Network Scientific Meeting in Rome, Italy, in 2018 (www.internationalecmonetwork.org/conferences).

Conventional Approaches to Minimizing VILI

The main focus of mechanical ventilation in ARDS is to provide adequate gas exchange while limiting injury to the organs (4), the contributors to which include barotrauma, volutrauma, atelectrauma, ergotrauma, myotrauma, and biotrauma (Figure 1) (5–9). Lung injury may be further exacerbated by spontaneous breathing efforts and patient–ventilator dyssynchrony with a consequent increase in transpulmonary pressures (10–12). V_T, plateau airway pressure, driving pressure, respiratory rate, inspiratory flow, and excessive positive end-expiratory pressure (PEEP) have all been implicated as contributors to VILI to varying degrees (4, 9, 13), though it remains unclear which of these parameters are most important in reducing injury. Driving pressure appears to be the ventilation variable that correlates most strongly with mortality (14), though a causal relationship between driving pressure and outcome has not been firmly established (14–17). Many of these factors have been incorporated into mathematical equations reflecting the amount of energy transferred from the ventilator to the respiratory system, referred to as "mechanical power" (13).

Volume- and pressure-limited ventilation (V_T of 4–8 ml/kg predicted body weight, frequently referred to as "6 ml/kg" because that is the initial goal after stabilization, and plateau airway pressure of $\leqslant$30 cm H_2O) and prone positioning have demonstrated survival benefits in ARDS (18–20), and they have been recommended in recent clinical practice guidelines (21). Additional strategies, including high levels of PEEP and, to a lesser degree, recruitment maneuvers, may likewise be beneficial, although the efficacy of these approaches has been called into question, given the results of a randomized controlled trial that found increased mortality in patients who were treated with a lung recruitment and titrated PEEP strategy (16, 22, 23). Although the ROSE (Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome) trial did not demonstrate a benefit from the addition of a fixed-dose, 48-hour infusion of neuromuscular blockade in patients with ARDS and a $Pa_{O_2}/F_{I_{O_2}}$ ratio $<$150 mm Hg (24), the use of neuromuscular blockade may nonetheless be considered on an individualized basis, particularly in the setting of ventilator dyssynchrony (e.g., double triggering), which may increase the propensity for VILI, or as needed for the implementation of prone positioning (25–28). Although not specifically addressed in this narrative review, a restrictive fluid management strategy may have additional benefits in ARDS (29).

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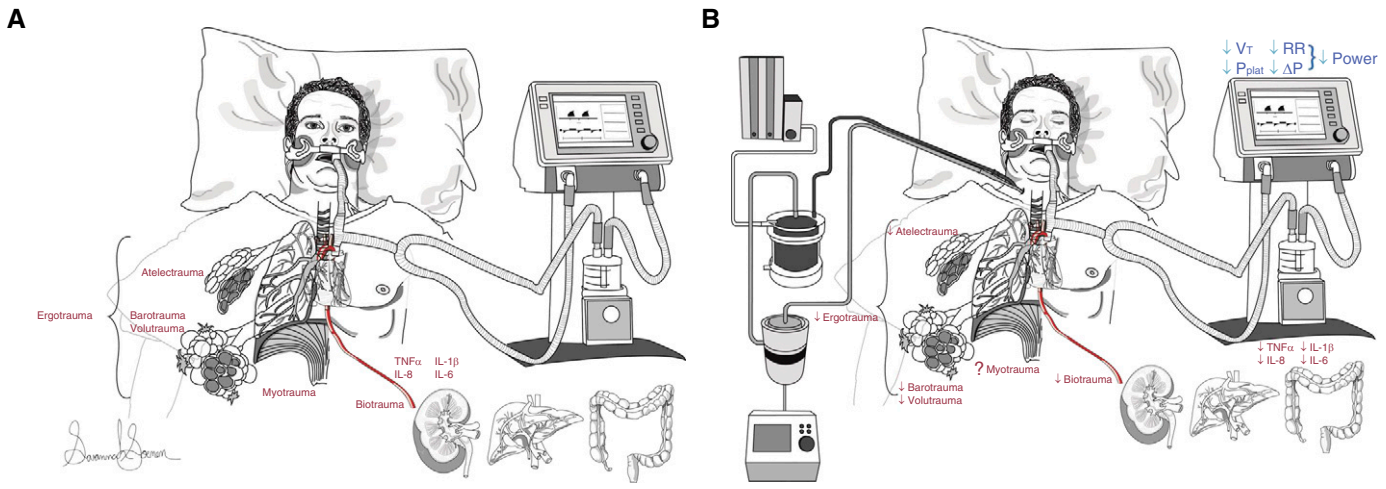

Figure 1. Potential effects of extracorporeal life support (ECLS) on ventilator-induced lung injury (VILI). (*A*) Invasive mechanical ventilation may cause VILI through multiple mechanisms, including atelectrauma, barotrauma, volutrauma, myotrauma, and biotrauma. (*B*) The addition of ECLS allows reductions in many of the contributors to VILI through decreases in V_T, respiratory rate, driving pressure, and plateau airway pressure while maintaining adequate gas exchange. The effect on certain parameters, such as myotrauma, will depend on the patient's respiratory effort and synchrony between the patient and ventilator. ECLS may help reduce myotrauma by minimizing excess respiratory drive. ΔP = driving pressure; Pplat = plateau airway pressure; RR = respiratory rate; TNFα = tumor necrosis factor-α. Illustration created by Savannah Soenen.

Rationale for Ultra–Lung-Protective Ventilation

Data Supporting Ultra–Lung-Protective Ventilation

Both preclinical and human data suggest that VILI continues to occur during ARDS despite adherence to best practice conventional ventilation management (30–32). Animal models have highlighted the injurious effects of cyclic alveolar stretch, particularly at high V_T or in the context of hyperoxemia (33–35). Frank and colleagues demonstrated that lung injury in a rat model of ARDS decreased when V_T was lowered from 12 ml/kg to 6 ml/kg, but lung injury appeared to be minimized even further when V_T was lowered to 3 ml/kg (30). *Post hoc* analysis of the ARMA (Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome) trial suggests that there is a consistent correlation between lower V_T, lower plateau airway pressures, and improved survival (31), and Needham and colleagues demonstrated that this relationship continues in a linear fashion below the traditional lung-protective V_T of 6 ml/kg (32).

Limitations in Achieving Ultra–Lung-Protective Ventilation

With no apparent lower limit to the mortality reduction associated with volume and pressure reductions during ARDS management (31, 32), it may be reasonable to conclude that V_T and airway pressure should be reduced below the current standard of care to minimize VILI and maximize outcomes. If V_T of 6 ml/kg (and corresponding plateau airway pressures ⩽30 cm H_2O) are considered "lung protective" (18), then perhaps even lower V_T (i.e., <4 ml/kg) and airway pressure (e.g., <25 cm H_2O) should be referred to as "ultra–lung-protective" ventilation. Respiratory rate, which from a VILI perspective may be viewed as the frequency with which the lung is exposed to injurious volumes and pressures, has likewise been proposed as a potential target for VILI reduction (13, 36, 37).

The main physiological barrier to achieving ultra–lung-protective ventilation in some patients with ARDS (particularly those with the most severe forms of ARDS) is the development of intolerable respiratory acidosis, which in turn often necessitates a high respiratory rate that may or may not be sufficient to mitigate the acidemia and may itself add to VILI. In fact, to maintain acceptable pH during the application of even traditional low V_T (6.2–6.5 ml/kg) during the ARMA trial, respiratory rates were substantially higher (29–30 breaths/min) than in the high-V_T control group (16–20 breaths/min) over the first 7 days of the study (18). The use of extracorporeal gas exchange offers an opportunity to achieve ultra–lung-protective ventilation, including reductions in respiratory rate, while mitigating the resultant respiratory acidosis. Of course, not all patients require ECLS to achieve ultra–lung-protective ventilation (38). However, without ECLS, this would be difficult to achieve in most patients with severe ARDS.

Extracorporeal Membrane Oxygenation and Extracorporeal Carbon Dioxide Removal in ARDS

Indications for Extracorporeal Membrane Oxygenation and Extracorporeal Carbon Dioxide Removal

Venovenous extracorporeal membrane oxygenation (ECMO) and extracorporeal carbon dioxide removal ($ECCO_2R$) are two related forms of ECLS that have the ability to support impairment in gas exchange (39). In both circumstances, venous blood is drained from a central vein via a cannula, pumped through a semipermeable membrane that permits diffusion of oxygen and carbon dioxide, and returned via a cannula to a central vein. ECMO, which uses high blood flow rates to both oxygenate the blood and remove carbon dioxide, may be considered in patients with severe ARDS with refractory hypoxemia or severe respiratory acidosis (1, 2). Because carbon dioxide removal is much more efficient than oxygenation, $ECCO_2R$ can be accomplished at relatively low blood flow

rates, although this approach will not effectively improve oxygenation (Figure 2) (40, 41). Lower blood flow rates permit the use of smaller cannulae for $ECCO_2R$ than would be required for ECMO (42), which theoretically provides a safer risk profile when compared with ECMO from the perspective of cannula-associated complications. However, a need for higher levels of anticoagulation with $ECCO_2R$ than with ECMO, given the lower blood flow rates (43), may be associated with higher—not lower—risks of complications (44, 45). The majority of $ECCO_2R$ is performed as venovenous $ECCO_2R$, but pumpless arteriovenous $ECCO_2R$ has also been reported, a method that introduces the additional risk of arterial cannulation and does not allow the same degree of control of extracorporeal blood flow ($\dot{Q}_E$) rates (46).

ECMO is supported by an increasing body of literature justifying various thresholds for its use in severe ARDS for the management of marked impairments in gas exchange (1, 26, 47, 48). There has been a steady rise in its use for these indications (49, 50). Identifying maximally protective ventilator management and gas exchange targets is essential to realizing the potential benefit of ECMO when it is employed in this context. In less severe ARDS, whether $ECCO_2R$ should be applied solely for the purpose of facilitating ultra–lung-protective ventilation is a subject of ongoing clinical investigation (*see* Table E2 in the online supplement) (40). More data are needed before $ECCO_2R$ can be recommended in less severe forms of ARDS for which ECMO itself is not otherwise indicated.

Ability of ECLS to Facilitate Ultra–Lung-Protective Ventilation

In an experimental study, Grasso and colleagues demonstrated the feasibility and potential impact of using $ECCO_2R$ to achieve isolated reductions in respiratory rates (from 30.5 to 14.2 breaths/min), with notable decreases in several inflammatory cytokines associated with VILI (36). Several prospective trials of ECLS in ARDS have demonstrated the feasibility of reducing various ventilator parameters while maintaining adequate gas exchange (36, 46, 51, 52). Most of these trials have employed $ECCO_2R$, but the results may be extrapolated to ECMO, which provides even greater gas exchange support. Terragni and colleagues used $ECCO_2R$ in patients with ARDS to facilitate reductions in plateau airway pressure from 29.1 to 25.0 cm H_2O (and V_T from 6.3 to 4.2 ml/kg) while correcting the resultant respiratory acidosis, with an associated reduction in pulmonary inflammatory cytokines (51). The Xtravent study randomized 79 patients with moderate to severe ARDS to standard mechanical ventilation or $ECCO_2R$-assisted ultra–lung-protective ventilation, and very low V_T (3.4 ml/kg) was achieved with marked reductions in driving pressure and normal pH maintained without an increase in respiratory rate (Table 1) (46).

A recent phase 2 international collaborative study of $ECCO_2R$ to facilitate ultra–lung-protective ventilation was performed in 95 subjects with moderate ARDS. Reductions in V_T from 6.0 to 4.2 ml/kg, in plateau airway pressure from 27.7 to 23.9 cm H_2O, and in respiratory rate from 27.4 to 23.5 breaths/min were achieved simultaneously, all while maintaining Pa_{CO_2} and pH within predefined acceptable ranges (Table 1) (52). The reductions in V_T and airway pressure led to a decrease in driving pressure from an average of 13.2 to 9.9 cm H_2O ($P = 0.001$) while maintaining a similar level of PEEP.

In the context of clinical practice, retrospective studies, patient-level meta-analyses, and a prospective multicenter study of high-volume ECLS centers all corroborate the findings of the aforementioned feasibility studies, wherein ECLS initiation is typically accompanied by reductions in V_T, plateau airway pressure, driving pressure, respiratory rate, and FI_{O_2}, with variable changes in PEEP and preservation of gas exchange (Table 1) (53–56). The LIFEGARDS (Mechanical Ventilation Management during ECMO for ARDS: An International Multicenter Prospective Cohort) international observational study enrolled 350 patients supported by ECLS across 23 ICUs with

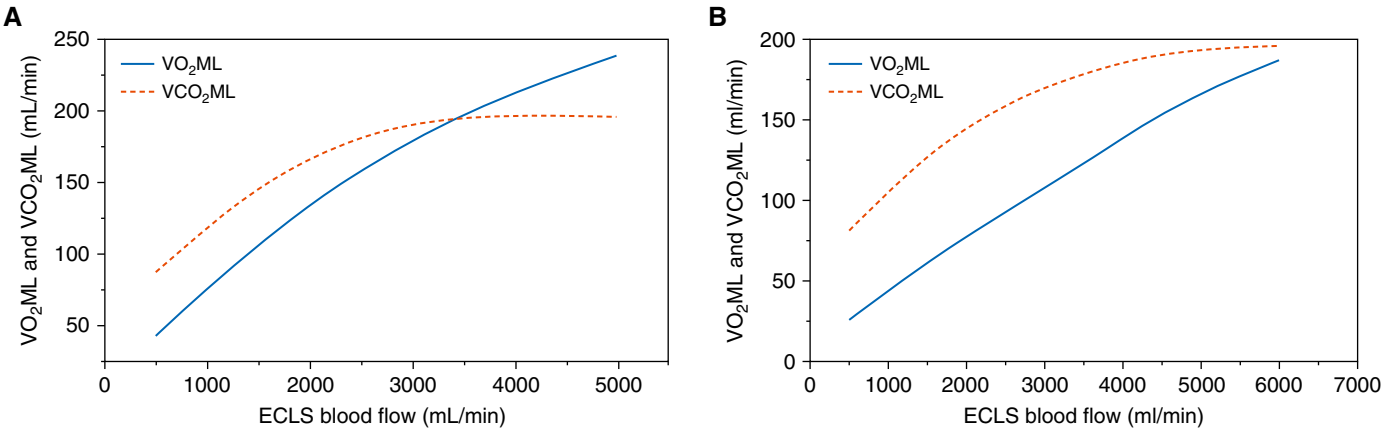

Figure 2. Mathematical model demonstrating the relationship between extracorporeal life support (ECLS) blood flow, $\dot{Q}$, oxygen delivery ($\dot{V}_{O_2}ML$), and carbon dioxide removal ($\dot{V}_{CO_2}ML$) through the membrane lung. Maximal rates of $\dot{V}_{CO_2}ML$ can be achieved at relatively low blood flow rates compared with those needed for $\dot{V}_{O_2}ML$. (*A*) Rates of $\dot{V}_{CO_2}ML$ and $\dot{V}_{O_2}ML$ at a $\dot{Q}$ of 5 L/min. Near-total $\dot{V}_{CO_2}ML$ is achieved at an ECLS blood flow rate of approximately 3 L/min. (*B*) Rates of $\dot{V}_{CO_2}ML$ and $\dot{V}_{O_2}ML$ through the membrane lung at a $\dot{Q}$ of 8 L/min. Near-total $\dot{V}_{CO_2}ML$ is achieved at an ECLS blood flow rate of approximately 5 L/min. This model assumes a sweep gas flow rate of 10 L/min, FI_{O_2} of 1.0, fraction of delivered oxygen to the membrane lung of 1.0, total $\dot{V}_{CO_2}$ of 200 ml/min, total $\dot{V}_{O_2}$ of 250 ml/min, Pa_{CO_2} maintained at 40 mm Hg, Hb of 10 g/dl, and recirculation of 15%. Graphs derived from www.ecmomodel.unimi.it with the help of Alberto Zanella on the basis of a previously published mathematical model (41).

Table 1. Ventilatory Parameters before and after Extracorporeal Life Support Initiation in Studies of ECLS for Acute Respiratory Distress Syndrome

	Retrospective Studies						Prospective Studies							
	Schmidt *et al.* (54)		Marhong *et al.* (55)		Serpa Neto *et al.* (53)		Xtravent (46)		EOLIA (1)		SUPERNOVA (52)		LIFEGARDS (56)	
	Before ECLS	After ECLS*	Before ECLS	After ECLS†	Before ECLS	After ECLS†	Before ECLS	After ECLS†	Before ECLS	After ECLS†	Before ECLS	After ECLS†	Before ECLS	After ECLS‡
V_T, ml/kg PBW	6.3	3.9	6.1	3.9	6.0	4.0	5.9	3.4	6.0	3.4	6.0	4.2	6.4	3.7
RR, breaths/min	22.0	15.0	—	—	21.9	17.8	22.4	22.2	30.4	23.1	27.4	23.5	26	14
V_E, L/min	8.8	3.6	—	—	9.1	5.0	9.9	5.8	—	—	10.2	5.9	10.2	3.5
PEEP, cm H_2O	13.0	12.0	14.0	12.0	13.7	12.9	16.1	17.1	11.7	11.2	13.6	14	12	11
Pplat, cm H_2O	32.2	26.4	32	25.5	31.1	26.2	29.0	25.1	29.8	24.4	27.7	23.9	32	24
ΔP, cm H_2O	19	13.7	18	13.5	17.7	13.7	12.9	8.0	17.8	13.2	13.2	9.9	20	14
Crs, ml/cm H_2O	23.2	19.9	22.7	19.4	26.8	23.2	34.4	32.2	25.0	20.1	—	—	24	19
$F_{I_{O_2}}$	0.96	0.60	0.99	0.40	0.90	0.69	0.62	0.54	0.96	0.50	—	—	1.0	0.5
Pa_{CO_2}, mm Hg	66.0	40.5	—	—	58.3	40.3	57.3	53.9	57	38	48	46.7	68	42
pH	7.24	7.41	—	—	7.27	7.39	7.34	7.38	7.24	7.37	7.34	7.39	7.24	7.4
$Pa_{O_2}/F_{I_{O_2}}$, mm Hg	67.0	—	61.0	—	72.6	152.5	152	154.5	73	—	168	168	71	—
Q_E, L/min	—	4.5	—	3.0	—	4.3	—	1.3	—	5.0	—	0.4	—	4.2

Definition of abbreviations: Crs = respiratory system compliance; ΔP = driving pressure; ECLS = extracorporeal life support; EOLIA = Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome trial; LIFEGARDS = Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: An International Multicenter Prospective Cohort trial; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pplat = plateau airway pressure; $\dot{Q}_E$ = extracorporeal blood flow rate; RR = respiratory rate; SUPERNOVA = Strategy of Ultraprotective Lung Ventilation with Extracorporeal CO_2 Removal for New-Onset Moderate to Severe Acute Respiratory Distress Syndrome trial.

*Average over Day 1 to Day 3 of ECLS.

†At 24 hours of ECLS.

‡Within first 2 days of ECLS.

experience in ECLS. An ultra–lung-protective ventilation strategy was largely applied: Driving pressure was maintained ≤15 cm H_2O, correlating with a decrease in mechanical power from 26.1 ± 12.7 J/min before ECLS to 6.6 ± 4.8 J/min during ECLS (56). Mechanical ventilation settings during the first two days of ECLS were not associated with mortality, in contrast to previous observations which suggested that decreased driving pressure and increased PEEP early in the course of ECLS were independently associated with reduced mortality (53, 54). This lack of association between early mechanical ventilation settings and outcomes indirectly suggests that once ultra–lung-protective ventilation (i.e., low driving pressure and very low power) has been efficiently implemented, the residual ventilation does not substantially influence outcome. A time-varying Cox model identified higher V_T and lower driving pressure over the duration of ECLS support, implying progressive improvement in static respiratory system compliance as being independently associated with lower 6-month mortality.

Optimizing Ventilator Settings during ECLS for ARDS

No large, prospective clinical trials comparing different ventilation strategies during ECLS for ARDS have been conducted, and thus no definitive standard of care exists. Available data, however, might offer valuable insights into what might be considered current best practices.

A preclinical swine study investigating the effect of mechanical ventilation strategies on lung injury in ARDS supported with ECMO found that a ventilation strategy with very low airway pressure, V_T, and respiratory rate (PEEP of 10 cm H_2O, driving pressure of 10 cm H_2O, V_T of ∼2 ml/kg, respiratory rate of 5 breaths/min) led to less histological lung injury than so-called nonprotective (PEEP of 5 cm H_2O, V_T of 10 ml/kg, respiratory rate of 20 breaths/min) or conventional protective (PEEP of 10 cm H_2O, V_T of 6 ml/kg, respiratory rate of 20 breaths/min) approaches (57).

A recent single-center, randomized crossover trial provided pilot data on the effect of ultra–lung-protective ventilation (maximum plateau airway pressure of 24 cm H_2O) with various combinations of PEEP (range, 5–20 cm H_2O) and driving pressure (range, 4–19 cm H_2O) on inflammatory cytokines in 16 patients receiving ECMO for severe ARDS (58). Compared with pre-ECMO standard-of-care conventional ventilation, strategies that combined higher PEEP with lower driving pressure demonstrated significant reductions in both plasma IL-6 and soluble receptor for advanced glycation end products. Of note, driving pressures of 12 and 4 cm H_2O correlated with mean V_T of 3.3 and 1.5 ml/kg, respectively, despite which pH and Pa_{CO_2} levels were maintained within the normal range.

The most rigorous controlled data for major clinical outcomes with ECMO in severe ARDS come from the EOLIA (Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome) trial (1), which, in combination with a *post hoc* Bayesian analysis (47) and a systematic review with meta-analysis (48), suggest improved mortality in patients supported with ECMO compared with patients receiving best practice conventional management strategies. The ventilation strategy used in EOLIA during ECMO limited plateau airway pressure to a maximum of 24 cm H_2O in conjunction with PEEP ≥10 cm H_2O (corresponding to a driving pressure ≤14 cm H_2O), respiratory rate of 10–30 breaths per minute, and $F_{I_{O_2}}$ of 0.3–0.5 (Table E1) (1). The subgroup of EOLIA with the greatest reduction in mortality consisted of those patients enrolled because of excessive ventilatory pressures and respiratory acidosis rather than for hypoxemia, although randomization was not stratified by inclusion criteria. It seems reasonable to propose that ECMO-supported patients be managed with ventilator settings that do not exceed the parameters used in the EOLIA trial or, alternatively, the CESAR (Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial, whose ECMO-facilitated ventilator settings were similar to those of EOLIA and whose data were included in the systematic review with meta-analysis (3, 48). Given the impact of V_T, driving pressure, and possibly respiratory rate on VILI, as well as the relative ease with which these variables can be reduced during ECMO, it may be advantageous to target lower volumes, pressures, and respiratory rates beyond those used in EOLIA (Table 2), but this remains unproven. The optimal PEEP for patients receiving ECLS is similarly unclear, and PEEP may require individualization based on a given patient's alveolar recruitability, pleural pressure, and hemodynamics (59). In the absence of data to the contrary, again a PEEP of at least 10 cm H_2O may be reasonably proposed on the basis of favorable outcomes with the strategy used in EOLIA, with consideration for higher PEEP in patients with morbid obesity. Beyond this, whether apneic oxygenation (i.e., optimized PEEP with no respiratory rate or driving pressure, so-called maximal lung rest) is better than tidal ventilation has yet to be determined.

Although ultra–lung-protective ventilation appears to be both achievable and beneficial for patients receiving ECLS for ARDS, the optimal targets of these parameters, how best to individualize these settings, how long to stay within the limits of these targets, whether adjunctive therapies (e.g., prone positioning and neuromuscular blockade) may be of additional benefit, when to wean patients from extracorporeal support, and the impact of these strategies on long-term outcomes are all areas that require further investigation (Table 3) (21, 60–63). Ongoing and upcoming randomized controlled trials may provide further insight into several of these topics (Table E2). Prone positioning during ECLS, which is the subject of a multicenter trial in the planning phase, is one area of particular interest, given that there is robust data for prone positioning during conventional ARDS management. However, the physiological effects of prone positioning may not necessarily be as impactful when ultra–lung-protective ventilation, and thus very low V_T, is applied, and there is added risk of ECLS cannula dislodgment during the maneuver itself. A study matching patients receiving prone positioning during ECMO for ARDS with those not receiving prone positioning suggested a benefit of being in the prone position. However, this practice remains investigational pending further evidence (64). Future trials of mechanical ventilation during ECLS for ARDS may benefit from enriching study populations with patients whose physiological parameters would suggest the greatest likelihood of detecting a response from the intervention (65).

Table 2. Suggested Initial Mechanical Ventilation Targets during ECLS for Acute Respiratory Distress Syndrome

Parameter	Target	Notes
Pplat*	⩽24 cm H_2O; may choose to go lower if feasible	
Driving pressure*	⩽14 cm H_2O	
V_T	Adjust for goal Pplat	Typically ⩽4 ml/kg PBW, often much lower
Respiratory rate†	⩽10 breaths/min	Typically only achieved when sedation, with or without NMBAs, is being used. Consider increased sweep flow to achieve, when appropriate
PEEP*	⩾10 cm H_2O	*See* text for circumstances that may warrant particularly high levels of PEEP
$F_{I_{O_2}}$*	0.3–0.5	Higher $F_{I_{O_2}}$ may be necessary if ECLS is inadequate for achieving acceptable levels of oxygenation Adequate oxygen delivery is the primary goal, not a particular Sa_{O_2}

Definition of abbreviations: ECLS = extracorporeal life support; EOLIA = Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome trial; NMBAs = neuromuscular blocking agents; PBW = predicted body weight; PEEP = positive end-expiratory pressure; Pplat = plateau airway pressure.
*These recommended targets are based on the ventilator protocol of the intervention arm of the EOLIA.
†The recommendation for respiratory rate below the lower limit of the EOLIA protocol is based on the presumption that lower respiratory rates are both more protective and achievable during ECLS.

Gas Exchange Targets during ECLS for ARDS

Recommendations

There are no evidence-based guidelines for the management of oxygenation, carbon dioxide, or pH in patients with ARDS supported with ECLS, and safe limits of hypoxemia and hypercapnia have not been firmly established. In the absence of data to the contrary, it is reasonable to use the gas exchange targets implemented in the EOLIA trial (Pa_{O_2} 65–90 mm Hg; Pa_{CO_2} <45 mm Hg) (1) as a default approach during ECLS until more specific data addressing these parameters are obtained. Previously established values from studies using conventional management strategies, including the ARMA approach, may also be appropriate (Table E1) (18, 66).

Potential Consequences of Extremes in Oxygen and Carbon Dioxide

Existing data have called attention to uncertainty about the tolerable lower and upper limits of oxygenation (67, 68), both of which may be relevant for patients receiving ECMO. Retrospective observational data of patients receiving venovenous ECMO for respiratory failure suggest increased mortality associated with both moderate hyperoxemia (Pa_{O_2} 101–300 mm Hg) and hypoxemia (Pa_{O_2} <60 mm Hg) 24 hours after ECMO initiation compared with near-normal oxygenation (Pa_{O_2} 60–100 mm Hg) (69). Other data suggest that the neurocognitive impact of prolonged hypoxemia (e.g., oxygen saturation as measured by pulse oximetry of 80% for up to 10 d) during ECLS for ARDS might be limited as long as tissue hypoxia (as assessed by blood lactate concentrations) is avoided (70, 71). However, such data must only be considered hypothesis generating for future studies.

An association between hyperoxemia (Pa_{O_2} >200 mm Hg) within the first 48 hours of ECLS initiation and increased mortality was also identified in a pediatric ECMO cohort, although this analysis was not limited to patients with respiratory failure and involved both venovenous and venoarterial ECLS (72). The same study reported an association between Pa_{CO_2} <30 mm Hg within the first 48 hours of ECLS and an increased rate of neurological events (72). Of note, the rapidity with which carbon dioxide is reduced after ECLS initiation has been implicated in the development of neurological complications and is an area that warrants further study (73).

Table 3. Suggested Areas for Future Research for ECLS in ARDS

Ventilator settings
Which ventilator parameters are most predictive of outcomes in ARDS?
How should PEEP be titrated, and is there a role for recruitment maneuvers during ECLS?
Adjunctive therapies
Is there a role for neuromuscular blockade during ECLS?
Is there a role for prone positioning during ECLS?
Gas exchange targets during ECLS
What are optimal oxygen, carbon dioxide, and pH targets during ECLS?
What is the impact of hyperoxemia during ECLS?
What is the consequence, if any, of rapid changes in carbon dioxide?
Spontaneous breathing
Which factors influence respiratory drive in patients with ARDS receiving ECLS?
Should we allow for spontaneous breathing during ECLS?
If so, does the timing matter relative to the onset of ARDS?
Should mechanical ventilation be maintained during ECLS?
If so, which should be weaned first, ECLS or mechanical ventilation?
Can ECLS facilitate a lung- and diaphragm-protective ventilation strategy?
How can we determine which patients require ECLS for this strategy?

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ECLS = extracorporeal life support; PEEP = positive end-expiratory pressure.

Special Considerations for Gas Exchange during ECLS: Hypoxemia under ECMO

The degree to which ventilator settings can be reduced while targeting oxygenation and ventilation goals will depend predominantly

on the amount of $ECCO_2R$ and oxygenation achieved via the extracorporeal circuit, in addition to the tolerance for accepting deviations from prespecified gas exchange targets. Certain physiological effects of ECLS on gas exchange may pose challenges to achieving these targets and warrant particular consideration.

In venovenous ECMO, extracorporeal gas exchange is provided in series with native gas exchange. Well-oxygenated blood returned to the venous system from the ECMO circuit then passes through the native pulmonary circulation before reaching the systemic circulation. The contribution of ECMO to systemic oxygenation is dependent on the proportion of $\dot{Q}_E$ relative to systemic blood flow ($\dot{Q}_S$); the greater the percentage of $\dot{Q}$ passing through the circuit, the greater the contribution to systemic oxygenation (Figure 3) (39, 41). This configuration has certain physiological consequences that determine whether mechanical ventilation is still required for gas exchange. Delivery of blood with high oxygen content to the pulmonary vasculature will attenuate the hypoxemic vasoconstriction associated with regions of the lung with low $\dot{V}/\dot{Q}$ ratios, which in turn may reduce right ventricular afterload and improve right ventricular function (74). However, in cases in which there is residual native lung function, the consequent pulmonary vasodilation may also increase the shunt fraction through the native lung, potentially diminishing the benefit derived from ECMO in terms of oxygenation (75).

High ECMO blood flow rates relative to native $\dot{Q}$ ($\dot{Q}_E/\dot{Q}_S$), which in turn require larger ECMO cannulae, together with minimization of recirculation (oxygenated blood taken back up by the extracorporeal circuit without having passed through the systemic circulation), may therefore be necessary to provide sufficient gas exchange to achieve additional lung-protective ventilation (42, 76). Methods to reduce recirculation to maximize systemic oxygenation have been described elsewhere (76).

Special Considerations for Gas Exchange during ECLS: Hypoxemia under $ECCO_2R$

By contrast, $ECCO_2R$ does not contribute meaningfully to oxygenation and may in fact exacerbate hypoxemia, requiring increases in PEEP and FI_{O_2}. There are two major mechanisms by which $ECCO_2R$ may lead to hypoxemia. If $ECCO_2R$ is used to achieve a decreased V_T, the lower V_T will lead to a decrease in tidal recruitment and mean airway pressure, resulting in worsened atelectasis and an increase in shunt fraction. This could be offset by an increase in PEEP to recruit lung units and increase oxygenation.

The second mechanism of hypoxemia is more complex and pertains to the reduction in native lung alveolar ventilation in response to the addition of $ECCO_2R$, if maintaining a constant Pa_{CO_2} (77, 78). Assume that carbon dioxide elimination is 200 ml/min through alveolar ventilation and that $ECCO_2R$ is able to remove 100 ml/min. If maintaining steady-state Pa_{CO_2}, the addition of $ECCO_2R$ will cause native lung alveolar ventilation to be reduced by half (from 200 ml/min to 100 ml/min), resulting in a marked reduction in Pa_{O_2} in the alveoli and, by extension, Pa_{O_2} in arterial blood. These changes are reflected in the alveolar gas equation:

$$PAO_2 = (P_{atm} - PH_2O) \times FIO_2 - PaCO_2/RER$$

where RER (respiratory exchange ratio) represents the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$ within the lung. RER is defined as $\dot{V}CO_2/\dot{V}O_2$. In the presence of $ECCO_2R$, $\dot{V}CO_2$ within the alveolar gas equation is now equal to native lung $\dot{V}CO_2$ ($\dot{V}CO_2NL$) minus $\dot{V}CO_2$ accomplished by the $ECCO_2R$ membrane (referred to as $\dot{V}CO_2ML$):

$$PAO_2 = (P_{atm} - PH_2O) \times FIO_2 - PaCO_2/[(VCO_2NL - VCO_2ML)/VO_2]$$

Assuming a typical RER of 0.8 ($\dot{V}CO_2NL$ = 200 ml/min; $\dot{V}O_2$ = 250 ml/min), an extracorporeal circuit with a $\dot{V}CO_2ML$ of 100 ml/min will lead to a halving of the RER (0.4; i.e., [200 − 100]/250, assuming that the oxygen added to the circulation by the extracorporeal circuit is negligible). According to the alveolar gas equation, this decrease in RER would lead to a marked decrease in Pa_{O_2}, which can be "corrected" by increasing FI_{O_2} (77, 78). Such an effect on Pa_{O_2} may also be mitigated by targeting a lower Pa_{CO_2} rather than maintaining it at the pre-$ECCO_2R$ level, thereby reducing Pa_{CO_2} in proportion to the RER.

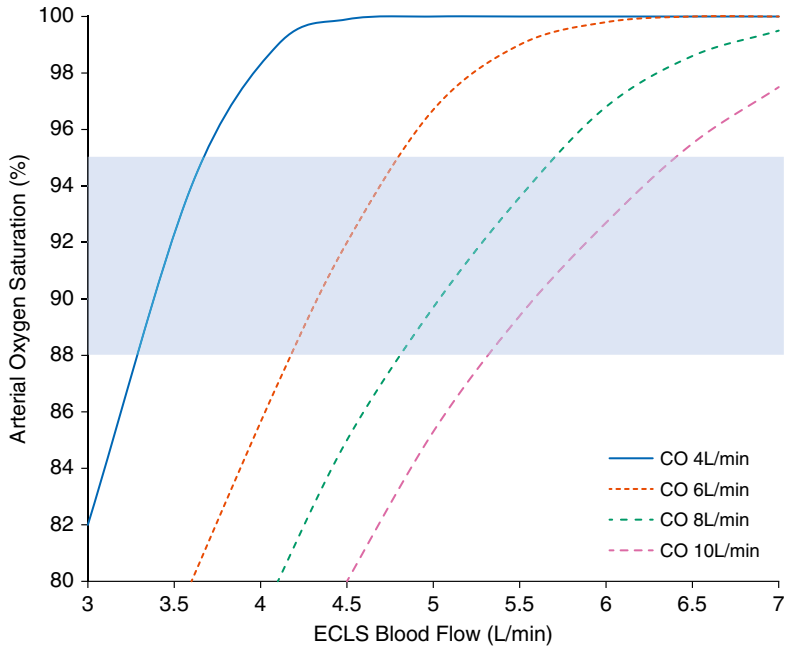

Figure 3. Mathematical model demonstrating the relationship between extracorporeal life support (ECLS) blood flow, $\dot{Q}$, and Sa_{O_2}. An increase in the ECLS blood flow/$\dot{Q}$ ratio leads to an increase in Sa_{O_2}. This model assumes a shunt fraction of 100%, fraction of delivered oxygen to the membrane lung of 1.0, Hb of 10 g/dl, and recirculation of 15%. Shaded blue bar indicates potential target Sa_{O_2} during ECLS. CO = $\dot{Q}$. Graphs derived from www.ecmomodel.unimi.it based on a previously published mathematical model (41).

Additional Areas for Research

The Role of Spontaneous Breathing

Up to this point, the discussion on optimal ventilator management during ECLS for ARDS has focused on the application of controlled mechanical ventilation with limits on airway pressures, V_T, and respiratory rates. Whether the allowance of spontaneous breathing, with or without ventilator support, during ECLS affords net benefit or harm likely depends, in part, on the patient's respiratory pattern, patient–ventilator dyssynchrony, pendelluft, the phase and duration of ARDS, and biological predisposition to mechanical injury (79). Vigorous spontaneous breathing with excessive V_T and $\dot{V}_E$ can lead to worsened lung injury through excessive transpulmonary pressure and transmural pulmonary vascular pressure, so-called patient self-inflicted lung injury (10, 11, 79, 80). One cannot, therefore, simply assume that a patient breathing spontaneously is protected from worsening lung injury, especially when the patient's drive to breathe is substantial.

The use of deep sedation (with or without neuromuscular blockade) during invasive mechanical ventilation may diminish patient–ventilator dyssynchrony and allow full control of invasive mechanical ventilation (12); yet, such an approach exposes patients to greater risk of diaphragmatic atrophy and adverse effects of increased doses of these drugs (e.g., delirium, inability to participate in physical therapy, delayed transition to spontaneous breathing, and liberation from invasive mechanical ventilation) (7). In addition, increased sedation can actually lead to worsening of some types of patient–ventilator dyssynchrony (e.g., reverse triggering) (81, 82). Allowing for patient inspiratory effort during invasive mechanical ventilation may reduce the risks of sedative and neuromuscular blocking agents and allow greater preservation of respiratory and peripheral muscle strength (83, 84), but in some patients, it may increase the risk of lung injury (12). How best to identify the optimal balance between minimizing sedation and avoiding VILI is unclear.

Extracorporeal support offers a potential means of controlling respiratory drive in select spontaneously breathing patients, and this has been demonstrated with variable success in patients with ARDS (85, 86). Titrating carbon dioxide removal to achieve an acceptable respiratory drive offers an opportunity to maintain safe spontaneous breathing (i.e., patient respiratory efforts that do not lead to unsafe dynamic stress and strain within the lung). This would alleviate the need for sedation and paralysis, permit the maintenance of respiratory effort to minimize diaphragm atrophy, and avoid the neurocognitive sequelae of heavy sedation. The feasibility of such regulation may also depend on the extent to which respiratory drive is subject to chemoreflex control, which in turn may depend on the duration and severity of ARDS. Such control, if feasible, opens the possibility of endotracheal extubation during extracorporeal support, which in turn would eliminate VILI altogether. Whether an initial strategy of ECLS and extubation (or avoidance of intubation) for ARDS is more favorable than controlled mechanical ventilation (with or without ECLS) has yet to be determined.

Weaning from Mechanical Support

For patients receiving both mechanical ventilation and ECLS who are recovering from ARDS and ready to be weaned from device support, whether to first decannulate or extubate depends on individual patient circumstances and clinical judgment because there are no high-quality data to guide decision making. Those with or at higher risk of developing ECLS complications (e.g., bleeding, hemolysis, and infection) may benefit from decannulation before extubation, whereas others at greater risk of ventilator-associated complications (e.g., patients with pneumothorax) or who require substantial amounts of sedation solely to maintain ventilator synchrony may benefit from a strategy that favors endotracheal extubation first.

Conclusions

The overall goal of invasive mechanical ventilation during ECLS for ARDS should be to decrease its intensity with the aim of reducing VILI and maximizing the potential benefit of ECLS. Precisely how particular ventilator variables should be adjusted has yet to be determined. In the interim, the EOLIA ventilator protocol during ECMO is a reasonable new minimum standard. Future studies should focus on more precisely delineating the best strategies for optimizing invasive mechanical ventilation during ECLS for ARDS. ■

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