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SYSTEMATIC REVIEW

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Mechanical ventilation during extracorporeal life support (ECLS): a systematic review

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Take-home message: ECLS facilitated provision of lung protective ventilation, as compared with baseline (pre-ECLS) settings, in the majority of studies included in our review. Use of "ultra"-protective tidal volumes and plateau pressures was common, but the benefit of this approach remains unclear. Future investigations should focus on establishing the optimal tidal volume, plateau pressure, and PEEP targets to be used for patients with ARDS supported on ECLS. The impact of these parameters on pulmonary recovery, VILI, and mortality remain to be established.

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Abstract *Purpose:* In patients with acute respiratory distress syndrome (ARDS), extracorporeal life support (ECLS) has been utilized to support gas exchange and mitigate ventilator-induced lung injury (VILI). The optimal ventilation settings while on ECLS are unknown. The purpose of this systematic review is to describe the ventilation practices in patients with ARDS who require ECLS. *Methods:* We electronically searched MEDLINE, EMBASE, CENTRAL, AMED, and HAPI (inception to January 2015). Studies included were randomized controlled trials, observational studies, or case series (≥4 patients) of ARDS patients undergoing ECLS. Our review focused on studies describing ventilation practices employed during ECLS for ARDS. *Results:* Forty-nine studies (2,042 patients) met our inclusion criteria. Prior to initiation of ECLS, at least one parameter consistent with injurious ventilation [tidal volume >8 mL/kg predicted body weight (PBW), peak pressure >35 cmH_2O (or plateau pressure >30 cmH_2O), or FiO_2 ≥0.8] was noted in 90 % of studies. After initiation of ECLS, studies reported median [interquartile range (IQR)] reductions in: tidal volume [2.4 mL/kg PBW (2.2–2.9)], plateau pressure [4.3 cmH_2O (3.5–5.8)], positive end-expiratory pressure (PEEP) [0.20 cmH_2O (0–3.0)], and FiO_2 [0.40 (0.30–0.60)]. Median (IQR) overall mortality was 41 % (31–51 %). *Conclusions:* Reduction in the intensity of mechanical ventilation in patients with ARDS supported by ECLS is common, suggesting that clinicians may be focused on reducing VILI after ECLS initiation. Future investigations should focus on establishing the optimal ventilatory strategy for patients with ARDS who require ECLS.

Keywords Critical care · Extracorporeal life support · Intensive care units · Mechanical ventilation · Acute respiratory distress syndrome · Systematic review

Introduction

Acute respiratory distress syndrome (ARDS) is a common cause of acute respiratory failure and is associated with substantial mortality [1–4]. While mechanical ventilation is life-saving, development of ventilator-induced lung injury (VILI) may have a detrimental effect on patient outcomes [5, 6]. While lung protective ventilation with pressure- and volume-limited strategies is associated with improved survival [7, 8], additional strategies to further mitigate VILI may be of value in facilitating lung healing.

Extracorporeal life support (ECLS) can provide gas exchange support in order to facilitate unloading of the pulmonary system [9]. ECLS can take on several configurations depending on therapeutic goals, but in patients with ARDS, these most commonly include venovenous (VV) extracorporeal membrane oxygenation (ECMO), venoarterial (VA) ECMO, or extracorporeal CO_2 removal ($ECCO_2R$) [9–11]. In addition to gas exchange support, ECLS may facilitate lung protective ventilation in patients in whom this may not have been achievable with conventional mechanical ventilation given the severity of lung injury [10, 12]. Due to extracorporeal support of gas exchange, ARDS patients may require less ventilatory support during ECLS. While some clinicians target "lung rest," with minimal ventilator settings [13, 14], there are no evidence-based guidelines for mechanical ventilation in patients supported by ECLS. This systematic review aims to describe mechanical ventilation practices in patients with ARDS supported with ECLS and associated outcomes.

Methods

Study population

Eligible studies included any randomized controlled trials (RCTs), observational studies, or case series ($\geq$4 patients) of adult patients (age $\geq$15 years) with ARDS who received any form of ECLS (VV, VA, or $ECCO_2R$) for respiratory failure. In studies with mixed patient populations supported with ECLS [i.e., chronic obstructive pulmonary disease (COPD), cardiac failure, etc.], data were only abstracted for patients with ARDS. As a requirement for inclusion, studies needed to report on mechanical ventilation parameters used during ECLS as well as mortality. In studies reporting on ARDS patients supported on VA-ECMO, data were abstracted under the assumption that these patients required ECLS for hemodynamic support in addition to respiratory failure.

Search strategy and study selection

We electronically searched MEDLINE, EMBASE, CENTRAL, AMED, and HAPI (from inception to January 2015) to identify studies for inclusion. Our search combined Medical Subject Headings (or appropriate controlled vocabulary) and keywords for ECLS and ARDS. There were no language or date restrictions applied. Three reviewers (J.D.M., L.M., T.T.) independently reviewed all titles and abstracts for possible inclusion. Full texts were reviewed for both definite and potentially eligible studies (J.D.M., L.M., T.T.). Any disagreements were resolved by group consensus (J.D.M., L.M., T.T., M.D., E.F.).

Data extraction and study quality

A custom-designed Excel spreadsheet (Microsoft Corporation, Redmond, WA) was used to store abstracted data on study design, patient characteristics, ECLS and mechanical ventilation parameters, complications, and outcomes (T.T., J.D.M., L.M.). Actual and targeted tidal volume, plateau pressures, positive end-expiratory pressure (PEEP), and/or fraction of inspired oxygen (FiO_2) following ECLS initiation were collected. Tidal volume data were abstracted only if reported in mL/kg predicted body weight (PBW). In studies where data were reported at multiple time points, we collected the data closest to 24 h following initiation of ECLS. All studies were assessed for evidence of bias using the Cochrane Collaboration risk of bias instrument [15], and we assessed study quality using the Newcastle Ottawa Scale for observational studies and Jadad Score for RCTs (Appendix 1).

Statistical analysis

Study-level data reporting on mean and median ventilator settings were summarized using median and interquartile range (IQR) and proportions as appropriate. We grouped studies describing mechanical ventilation practices in patients on VV-ECMO with studies where multiple ECLS modalities were used (labeled as mixed ECLS). Conversely, studies focusing on $ECCO_2R$ exclusively were analyzed separately in order to compare and contrast ventilator strategies between groups. A predefined sensitivity analysis was conducted in order to restrict analysis to studies conducted in the lung protective era, defined as the period following the publication of the ARDSNet ARMA study (i.e., after the year 2000). Injurious ventilation was defined as ventilation using tidal volume >8 mL/kg PBW, peak pressures >35 cmH_2O, plateau pressures >30 cmH_2O or FiO_2 >0.80. Finally, crude mortality was analyzed according to quartiles of plateau pressure, median tidal volume, and both median tidal volume and plateau pressure in studies reporting on both parameters from studies from the lung protective ventilation era.

Results

Literature search

The electronic search retrieved 2,677 citations, of which 99 full texts were retrieved for further adjudication (Fig. 1). Forty-nine studies (2,042 patients) fulfilled the inclusion criteria, including 3 RCTs and 46 observational studies [13, 16–56]. Twenty-one studies (777 patients) included patients on VV-ECMO alone, 10 studies (353 patients) included patients on $ECCO_2R$ alone, and the remaining 18 studies (924 patients) included mixed configurations, in which the majority of patients (16 studies, 883 patients) were predominantly supported by VV-ECMO. Two remaining studies used both VV- and VA-ECMO (1 study, 31 patients) or both VV and $ECCO_2R$ (1 study, 10 patients) (Appendix 1). Since the use of VV-ECMO predominated in these studies, it was felt that the aim of mechanical ventilation would be similar, with the selection of a particular configuration based on patient or clinical factors (i.e., use of VA-ECMO for concomitant ARDS and circulatory shock in the setting of severe sepsis).

Baseline characteristics along with initial ECLS settings are provided in Table 1. The most common cause of ARDS was bacterial (847 patients) and viral (388 patients) pneumonia, of which the majority of viral causes were influenza A (H1N1).

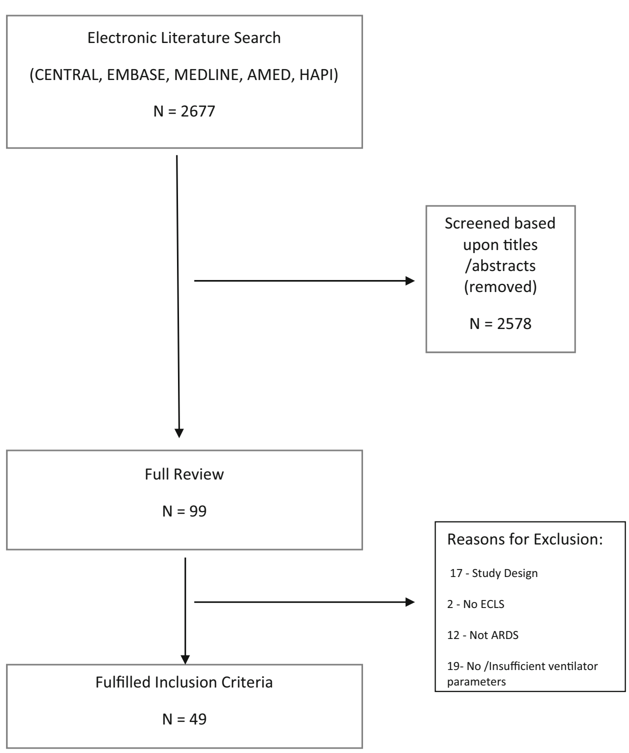

Fig. 1 Flow diagram of search strategy

Peripheral cannulation was used in the majority of cases and most commonly involved the femoral and internal jugular veins, or in the case of VA-ECMO, the femoral artery. The majority of programs (76 %) used activated clotting time (ACT) as their anticoagulation target.

Mechanical ventilation prior to initiation of ECLS

Across all studies, at least one ventilator setting was provided prior to initiation of ECLS (Table 2). Before initiation of ECLS, patients were ventilated using median (IQR) tidal volume 6.2 mL/kg PBW (5.9–6.7 mL/kg PBW), plateau pressure 32 cmH_2O (30.0–33.7 cmH_2O), PEEP 13 cmH_2O (12.0–15.0 cmH_2O), and FiO_2 0.99 (0.80–1.00). Ninety percent of studies reported injurious ventilation prior to ECLS initiation. These results were similar across mixed ECLS and $ECCO_2R$ studies.

Adjunctive therapies and indications for ECLS

The use of adjunctive therapies was described in 20 studies (836 patients). Three hundred and two patients underwent prone positioning, 369 patients received inhaled pulmonary vasodilators, and 32 patients were placed on high-frequency oscillation before use of ECLS. Twenty-five studies (647 patients) specified hypoxemia to be the primary indication for initiating ECLS, 1 study (8 patients) cited hypercapnia to be the primary indication, and 10 studies (540 patients) reported both hypoxemia and hypercapnia to be the indication for ECLS.

Mechanical ventilation after initiation of ECLS

Mechanical ventilatory settings were reduced across all studies after initiation of ECLS (Table 2). Injurious ventilation decreased from 90 % (29/32 studies, 1,291 patients) to 18 % (8/44 studies, 457 patients) after ECLS initiation.

Mixed ECLS studies

Of the 39 mixed ECLS studies, 15 reported tidal volume, 16 reported plateau pressure, 32 reported PEEP, and 26 reported FiO_2 following initiation of ECLS. After initiation of ECLS, 14 studies (713 patients) reported mean tidal volume $\leq$6 mL/kg PBW, while 7 studies (550 patients) reported mean tidal volume $\leq$4 mL/kg PBW. PEEP ranged between 5 and 10 cmH_2O in 15 studies (705 patients), 11 and 15 cmH_2O in 12 studies (586 patients), and >15 cmH_2O in 5 studies (59 patients). Plateau pressure $\leq$30 cmH_2O was observed in 13 studies (685 patients) and $\leq$25 cmH_2O in 7 studies (332 patients).

Table 1 Baseline characteristics

	All ECLS (2,042 patients, 49 studies) Median (IQR)	Mixed ECLS (1,689 patients, 39 studies) Median (IQR)[a]	$ECCO_2R$ (353 patients, 10 studies) Median (IQR)
Age (years)	39.0 (33–48)	39.0 (34.0–47.0)	38.5 (27.0–52.0)
APACHE II score	20.0 (18.0–23.9)	20.0 (18.5–24.5)	18.0 (18.0–18.0)
Lung injury score	3.5 (3.3–3.6)	3.5 (3.4–3.6)	3.2 (2.8–3.5)
PaO_2/FiO_2 ratio	61.0 (56.0–76.0)	60.0 (54.9–67.0)	81.5 (69.0–126.0)
Pneumonia ARDS	51 %	49 %	38 %
Adjunctive therapy used prior to ECLS[b]	41 %	56 %	20 %
Days on mechanical ventilation prior to ECLS	3.9 (3.0–86.4)	3.6 (2.0–5.0)	8.0 (4.0–9.1)
ECLS details			
Blood flow rate (L/min)	3.0 (1.8–4.4)	4.3 (2.8–4.5)	1.4 (1.3–2.4)
Sweep gas flow rate (L/min)	6.5 (5.5–10.0)	6.0 (5.0–6.5)	11.0 (10.0–11.0)

APACHE Acute Physiology and Chronic Health Evaluation, *ARDS* acute respiratory distress syndrome, *ECLS* extracorporeal life support, *$ECCO_2R$* extracorporeal CO_2 removal, *IQR* interquartile range, *VV* venovenous

[a] Mixed modality includes 33 studies, the predominant modality of which was venovenous extracorporeal membrane oxygenation

[b] Adjunctive therapy—high-frequency oscillation, prone positioning, inhaled pulmonary vasodilators, combination of rescue modalities explicitly mentioned

Conversely, tidal volumes >6 mL/kg PBW were observed in only 1 study (49 patients), and plateau pressures remained >30 cmH_2O in only 3 studies (89 patients). $FiO_2 \geq 0.80$ was reported in no studies after patients were placed on ECLS.

$ECCO_2R$

Of the 10 $ECCO_2R$ studies, 4 reported tidal volume, 2 reported plateau pressure, 8 reported PEEP, and 5 reported FiO_2 following initiation of ECLS. While on $ECCO_2R$, all studies (119 patients) achieved tidal volume ≤6 mL/kg PBW and 2 studies (47 patients) targeted tidal volume ≤4 mL/kg PBW. PEEP between 10 and 15 cmH_2O was reported in 3 studies (120 patients), while 5 studies (172 patients) used PEEP >15 cmH_2O. Two studies (58 patients) reported plateau pressure ≤30 cmH_2O while ventilating patients on $ECCO_2R$.

Interestingly, no studies reported tidal volume >6 mL/kg PBW after $ECCO_2R$ was initiated. Only 1 study (90 patients) reported using a $FiO_2 \geq 0.80$.

Mechanical ventilation post-lung protective era

Across 33 studies (1,505 patients) published after the year 2000 [8], mechanical ventilation parameters before and after initiation of ECLS were comparable (Table 3).

Mortality

The median (IQR) mortality reported across all studies was 41 % (31–51 %). The median (IQR) mortality was similar for studies using mixed ECLS [40 % (32–50 %)] but was slightly higher when restricted to studies examining $ECCO_2R$ exclusively [51 % (27–57 %)].

When mortality was stratified according to quartiles of plateau pressure following ECLS, the lowest quartile of plateau pressure (19–22 cmH_2O) was associated with a lower crude mortality [28 % (15–45 %)] as compared with the highest quartile of plateau pressure [31–36 cmH_2O; mortality 46 % (45–50 %)]. Similarly, a tidal volume below the median tidal volume following ECLS initiation (≤4 mL/kg) was associated with a lower mortality [29 % (18–50 %) versus 39 % (31–47 %)] compared with those with tidal volumes >4 mL/kg. Mortality was lowest in studies which achieved a combined tidal volume ≤4 mL/kg and plateau pressure ≤26 cmH_2O as compared with studies with tidal volume between 4 and 6 mL/kg and plateau pressure between 26 and 30 cmH_2O [23 %(15–34 %) versus 45 % (14–49 %)] (Table 4).

Discussion

Although recommendations for ventilation strategies during ECLS [10] have been promulgated (Table 5), this is the first systematic review (49 studies, 2,042 patients) to summarize ventilation practices in patients with ARDS supported on ECLS. This review demonstrates several ways that ECLS may help to mitigate VILI in ARDS. Across these studies, potentially injurious ventilation was present in almost all studies prior to ECLS. In addition, median tidal volumes across most studies reflected an "ultra" lung protective approach of ≤4 mL/kg PBW and

Table 2 Pre–post extracorporeal life support mechanical ventilation settings

	Tidal volume (mL/kg PBW)			Plateau pressure (cmH_2O)			PEEP (cmH_2O)			FiO_2			Mortality
	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	
All ECLS studies (49)	6.2 (5.9–6.7) 12 studies	4.0 (3.0–6.0) 19 studies	2.4 (2.1–2.9)	32.0 (30.0–33.7) 12 studies	26.0 (22.0–30.0) 18 studies	4.3 (3.5–5.8)	13 (12.0–15.0) 33 studies	12.0 (9.6–14.5) 40 studies	0.20 (0.0–3.0)	0.99 (0.80–1.00) 18 studies	0.40 (0.35–0.50) 31 studies	0.40 (0.30–0.60)	0.41 (0.31–0.51) 48 studies
Mixed ECLS studies (39)	6.1 (6.0–6.5) 8 studies	4.2 (3.1–6.0) 15 studies	2.2 (1.0–2.6)	32.0 (31.0–33.0) 9 studies	26.2 (23.0–30.0) 16 studies	4.3 (2.7–5.9)	13 (12.0–15.0) 24 studies	11.8 (9.2–13.0) 32 studies	1.0 (0–3.9)	1.00 (0.99–1.00) 11 studies	0.40 (0.32–0.40) 26 studies	0.56 (0.40–0.60)	0.40 (0.32–0.50) 38 studies
$ECCO_2R$ studies (10)	6.3 (6.0–7.8) 4 studies	3.5 (2.9–4.2) 4 studies	3.2 (2.6–4.2)	29.0 (22.1–35.0) 3 studies	24.4 (18.7–30.0) 2 studies	4.3 (3.5–5.0)	13.2 (11.7–16.1) 9 studies	16.6 (13.5–18.5) 8 studies	−3.9 (−6.0–0.20)	0.70 (0.50–0.70) 7 studies	0.70 (0.50–0.70) 5 studies	0.30 (0.20–0.30)	0.51 (0.27–0.57) 5 studies

All values are median (IQR) unless otherwise stated. Number of studies listed below are the number of studies for which sufficient data were available

Delta median values obtained by combining the delta of the mechanical ventilation parameters of studies which reported both pre-ECLS values and post-ECLS values

$ECCO_2R$ extracorporeal CO_2 removal, *IQR* interquartile range, *LPV* lung protective ventilation, *PEEP* positive end-expiratory pressure, *TV* tidal volume, *VV* venovenous ECMO studies (including a few mixed studies)

Table 3 Pre–post extracorporeal life support mechanical ventilation settings (post-lung protective era, >2000)

	Tidal volume (mL/kg PBW)			Plateau pressure (cmH_2O)			PEEP (cmH_2O)			FiO_2			Mortality
	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	Pre-ECLS	Post-ECLS	DELTA	
All ECLS studies (33)	6.1 (5.9–6.6) 11 studies	3.9 (3.0–5.0) 17 studies	2.3 (1.6–2.9)	32.0 (30.0–33.7) 12 studies	25.5 (22.0–30.0) 16 studies	4.3 (3.5–5.8)	14.0 (12.3–16.1) 21 studies	12.0 (9.2–14.0) 26 studies	1.0 (0–2.8)	0.99 (0.89–1.00) 11 studies	0.40 (0.30–0.50) 21 studies	0.36 (0.30–0.60)	0.40 (0.30–0.50) 34 studies
Mixed ECLS studies (28)	6.2 (5.9–6.5) 8 studies	4.1 (3.1–6.0) 14 studies	2.2 (1.0–2.6)	32.0 (31.0–33.0) 9 studies	25.5 (22.0–30.0) 14 studies	4.3 (2.8–5.9)	14.0 (13.0–16.0) 16 studies	12.0 (9.0–13.5) 22 studies	1.0 (0–3.0)	1.00 (0.99–1.00) 6 studies	0.40 (0.30–0.50) 17 studies	0.54 (0.40–0.70)	0.38 (0.31–0.49) 27 studies
$ECCO_2R$ studies (5)	6.1 (5.9–6.6) 3 studies	3.0 (2.7–4.4) 3 studies	2.9 (2.2–3.4)	29.0 (22.1–35.0) 3 studies	24.5 (18.7–30.0) 2 studies	4.3 (3.5–5.0)	15.0 (12.3–16.1) 5 studies	15.1 (13.1–16.6) 4 studies	−2.0 (−4.9–0.5)	0.80 (0.70–1.00) 5 studies	0.70 (0.60–0.75) 4 studies	0.30 (0.20–0.30)	0.49 (0.18–0.54) 5 studies

All values are median (IQR) unless otherwise stated. Number of studies listed below are the number of studies for which sufficient data were available

Delta median values obtained by combining the delta of the mechanical ventilation parameters of studies which reported both pre-ECLS values and post-ECLS values

$ECCO_2R$ extracorporeal CO_2 removal, *IQR* interquartile range, *LPV* lung protective ventilation, *PEEP* positive end-expiratory pressure, *TV* tidal volume, *VV* venovenous ECMO studies (including a few mixed studies). Delta values are only from those studies that reported on both pre and post parameters

Table 4 Mortality stratified according to plateau pressure quartiles and median tidal volume

	Mortality, median (IQR)	No. studies (patients)
Plateau pressure following ECLS		
Plateau pressure quartile 1 (19–22 cmH_2O)	0.28 (0.15–0.45)	5 (177)
Plateau pressure quartile 2 (23–25.5 cmH_2O)	0.41 (0.40–0.42)	2 (154)
Plateau pressure quartile 3 (25.6–30 cmH_2O)	0.45 (0.29, 0.50)	7 (404)
Plateau pressure quartile 4 (31–36 cmH_2O)	0.46 (0.45–0.50)	3 (89)
Tidal volume following ECLS		
Tidal volume ≤4.0 mL/kg	0.29 (0.18–0.50)	10 (618)
Tidal volume >4.0 mL/kg	0.39 (0.31–0.47)	8 (253)
Tidal volume and plateau pressure (PP)		
Tidal volume ≤3.9, PP ≤25.5[a]	0.23 (0.15–0.34)	4 (239)
Tidal volume 4–6, PP 26–30	0.45 (0.14–0.49)	3 (91)

IQR interquartile range, *PP* plateau pressure

[a] Median values from post-lung protective ventilation era studies

Table 5 Summary of mechanical ventilation protocols in previous randomized controlled trials, organizations or upcoming trials

Study/organization	Design	Protocol
Peek et al. [13]	Randomized controlled trial venovenous ECMO 2009	Peak inspiratory pressure 20–25 cmH_2O PEEP 10–15 cmH_2O Respiratory rate 10 breaths/min FiO_2 0.30
Bein et al. [57]	Randomized controlled trial $ECCO_2R$ 2013	Tidal volumes 3 mL/kg/PBW PEEP (ARDSNet "high-PEEP/FiO_2" table) Respiratory rate 10–25 breaths/min with inspiratory/expiratory ratio of 1:1
Extracorporeal Life Support Organization Adult Respiratory Failure Supplement to General Guidelines, December 2013 [73]	Guidelines venovenous ECMO 2013	Goals first 24 h: (moderate/heavy sedation) Pressure control 25 PEEP 15 FiO_2 0.50 Respiratory rate 5 breaths/min Inspiratory/expiratory ratio 2:1 After 24–48 h (minimal/moderate sedation, stable hemodynamics): Pressure-controlled ventilation 20/10 FiO_2 0.20–0.40 RR 5 breaths/min plus spontaneous breaths Inspiratory/expiratory ratio 2:1 After 48 h (no/minimal sedation) Pressure-controlled ventilation as above or continuous positive airway pressure 20 plus spontaneous breathing Tracheostomy or extubated within 3–5 days
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA study, ClinicalTrials.gov NCT01470703) [74]	Randomized controlled trial venovenous ECMO trial underway	Volume-assist control mode Tidal volume lowered to obtain plateau pressure <25 cmH_2O PEEP ≥10 cmH_2O, FiO_2 0.30–0.60 RR 10–30 breaths/min or APRV mode with high pressure level <25 cmH_2O and low pressure level ≥10 cmH_2O

APRV airway pressure release ventilation, *ECMO* extracorporeal membrane oxygenation, *FiO_2* fraction of inspired oxygen, *PEEP* positive end-expiratory pressure, *RR* respiratory rate

achievement of plateau pressures ≤30 cmH_2O. We speculate that these results suggest that clinicians were unable to achieve adequate gas exchange prior to initiation of ECLS without using tidal volumes and airway pressures outside of the lung protective range. Mortality was lower in the groups of patients who had a lower intensity of applied ventilation following ECLS initiation.

While ECLS can help facilitate a reduction in ventilation intensity, optimal targets for tidal volume, plateau pressure, PEEP, and FiO_2 have not been established beyond those from the ARDS Network ARMA trial [8]. Recent evidence by Hager and colleagues demonstrated a dose–response relationship between day-1 plateau pressures and mortality in patients with ARDS [58]. They showed that no "safe" threshold for plateau pressure exists, with lower plateau pressure associated with lower mortality [57]. Terragni and colleagues demonstrated ongoing tidal hyperinflation, an increase in lung inflammatory biomarkers, and a longer duration of ventilation in 33 % of patients with severe ARDS despite being ventilated with tidal volumes of 6 mL/kg PBW [58]. Increasing evidence suggests that these patients may benefit from even lower tidal volumes [56, 59], but the optimal target remains unclear. While ventilation with "ultra"-protective volumes has not demonstrated a definitive mortality benefit, it has been reported to reduce pulmonary inflammation and potentially increase ventilator-free days in patients with $PaO_2/FiO_2 \leq 150$ [56, 58, 60].

Mechanical ventilation during ECLS appears to have an important impact on mortality. A study by Pham and colleagues illustrates the importance of mechanical ventilation practices in patients requiring VV ECMO for H1N1-induced ARDS [43]. It demonstrated that a lower day-1 plateau pressure following ECMO initiation was independently associated with survival and concluded that targeting "ultra"-protective tidal volumes aimed at minimizing plateau pressure may be required to improve outcome [43]. This conclusion is further corroborated by a recent review by Schmidt and colleagues, which recommends limiting tidal volume to <4 mL/kg PBW, targeting a plateau pressure <25 cmH_2O, and alveolar recruitment with the use of PEEP while supporting ARDS patients on ECLS [10].

A recent international survey of centers registered with the Extracorporeal Life Support Organization (ELSO) reported on variation in ventilation practices among patients supported on ECLS for acute respiratory failure [14]. It showed that the majority of centers used a controlled mode of mechanical ventilation in order to target lung protective tidal volumes and moderate levels of PEEP. Centers responding to the survey used VV-ECMO to provide "lung rest" and preferentially weaned VV-ECMO before mechanical ventilation. Of note, 31 % of centers reported using tidal volumes <4 mL/kg PBW while ventilating patients on VV-ECMO [14]. In our review, the initiation of ECLS corresponded with an observed reduction in tidal volume and plateau pressure, although clinicians seem to have placed greater emphasis on tidal volume reductions while ventilating patients on ECLS. These findings seem to suggest that ECLS permitted a reduction in tidal volume in order to limit plateau pressures to lung protective, or even "ultra"-protective ranges. Alternatively, this may reflect a belief that tidal volume has a greater impact on mortality reduction in the setting of ARDS, though this remains controversial [61].

While PEEP and FiO_2 decreased across the mixed ECLS studies, an increase in PEEP and no change in FiO_2 were noted in the $ECCO_2R$ studies, reflecting the possible atelectasis that follows isolated CO_2 clearance [62, 63]. In the setting of $ECCO_2R$, application of PEEP to maintain alveolar recruitment and oxygenation is required, as $ECCO_2R$ is unable to generate sufficient blood flow to facilitate oxygenation [63]. Conversely, use of PEEP to improve oxygenation and reduce alveolar strain is not required in VV/VA-ECMO. Instead, PEEP may be used to promote lung healing by preventing pulmonary vascular leakage and macrophage activation [64–67]. In patients with severe ARDS, use of higher PEEP may be limited by high plateau pressure if sufficiently large tidal volumes are needed for adequate gas exchange. In facilitating lower tidal volumes, ECLS enables more room to apply an open lung ventilatory strategy [68]. The optimal PEEP target for patients supported on ECLS remains unclear at this point in time as no data are available to guide clinicians. More information may become available, as the impact of tidal ventilation and the optimal level of PEEP on VILI, physiological parameters, and cardiac function will be evaluated in the Strategies for Optimal Lung Ventilation during VV-ECMO for ARDS (SOLVE-ARDS) study (ClinicalTrials.gov NCT01990456).

There are several limitations to this review. First, we were able to identify only three RCTs describing ventilation strategies during ECLS [13, 52, 56]. This limited our ability to construct a meta-analysis establishing optimal ventilation targets in these patients given that these studies did not compare mechanical ventilation strategies. Since mechanical ventilation during ECLS may have important implications, our review provides a systematic summary of all of the currently available data. Next, detailed data on tidal volume in mL/kg PBW and plateau pressure were available in less than 50 % of the studies, with most studies reporting absolute tidal volume (mL) and peak inspiratory pressures. Since these values are not comparable with tidal volume (in mL/kg PBW and plateau pressure), we elected to exclude them from this analysis. Median values and interquartile ranges were used to summarize data from the studies that were included for analysis. Due to the heterogeneous design of these studies, these values should be interpreted cautiously as a general overview of the parameters described. While this review was able to separate studies examining $ECCO_2R$ exclusively, it was unable to separate patients treated with VV-ECMO and VA-ECMO to look for differences in ventilation strategy. For studies combining VV-ECMO and VA-ECMO, it is conceivable that ventilation goals were similar, but patients differed with respect to other factors (e.g., hemodynamic stability). Furthermore, the findings of this investigation would have been more informative if they included information regarding the mode of ventilation, as this can influence the achievement of ventilation targets (i.e., low plateau pressure versus low tidal volume) and weaning [9, 69–71]. Finally, the crude mortality data are likely confounded by a number of factors, and these results should be interpreted as hypothesis-generating. One could postulate that the lower mortality noted in the lower-intensity ventilation groups is because they had a less severe form of ARDS, thus allowing them to achieve lower-intensity ventilation. We feel the trend noted in the results reflecting an association between lower intensity of ventilation (beyond traditional lung protective targets) and an even lower mortality is intriguing and should be further investigated through prospective means in the context of ECLS.

Conflicts of interest The authors declare that they have no conflict of interest.

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