


REVIEW



# Extracorporeal life support for adults with acute respiratory distress syndrome

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## Abstract

Extracorporeal life support (ECLS) can support gas exchange in patients with the acute respiratory distress syndrome (ARDS). During ECLS, 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. Two related forms of ECLS are used. Venovenous extracorporeal membrane oxygenation (ECMO), which uses high blood flow rates to both oxygenate the blood and remove carbon dioxide, may be considered in patients with severe ARDS whose oxygenation or ventilation cannot be maintained adequately with best practice conventional mechanical ventilation and adjunctive therapies, including prone positioning. Extracorporeal carbon dioxide removal (ECCO<sub>2</sub>R) uses lower blood flow rates through smaller cannulae and provides substantial CO<sub>2</sub> elimination (~20–70% of total CO<sub>2</sub> production), albeit with marginal improvement in oxygenation. The rationale for using ECCO<sub>2</sub>R in ARDS is to facilitate lung-protective ventilation by allowing a reduction of tidal volume, respiratory rate, plateau pressure, driving pressure and mechanical power delivered by the mechanical ventilator. This narrative review summarizes physiological concepts related to ECLS, as well as the rationale and evidence supporting ECMO and ECCO<sub>2</sub>R for the treatment of ARDS. It also reviews complications, limitations, and the ethical dilemmas that can arise in treating patients with ECLS. Finally, it discusses future key research questions and challenges for this technology.

**Keywords:** Acute respiratory failure, Extracorporeal membrane oxygenation, Mechanical ventilation, Outcome

## Introduction

In a prospective international study conducted in 459 ICUs across 50 countries, acute respiratory distress syndrome (ARDS) represented 10.4% of total intensive care unit (ICU) admissions [1]. Over the past two decades, in-hospital mortality from ARDS has remained very high at approximately 40% [1]. Despite strong experimental and clinical evidence [2] that lung protection improves outcomes in ARDS, it remains underutilized [1].

With the ultimate goal of protecting the injured lung, and improving oxygenation, there has been increasing adoption of extracorporeal life support (ECLS) in adult patients with very severe ARDS. Advances in supportive care, innovations in technologies and insights from

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recent clinical trials have contributed to improved outcomes and a renewed interest in the scope and use of ECLS [3–5].

This narrative review provides a summary of some physiological concepts related to ECLS, as well as the rationale and evidence supporting the two main forms of ECLS for the treatment of ARDS: extracorporeal membrane oxygenation (ECMO) and extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R). We also highlight evidence on complications, limitations, and the ethical dilemmas that can arise in treating patients with ECLS. Finally, we discuss future key research questions and challenges for this technology.

**What is ECLS and how does it provide gas exchange?**

**Extracorporeal life support**

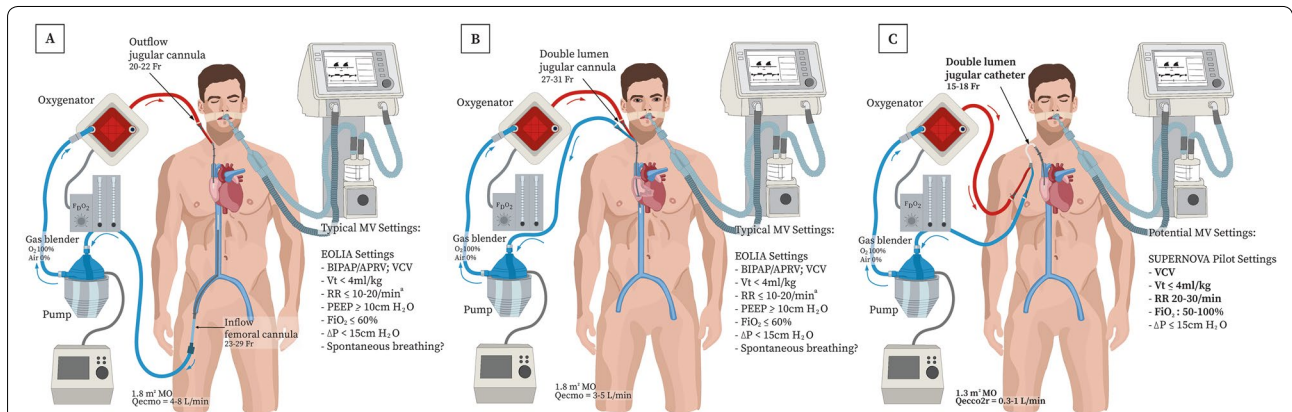
Membrane oxygenators are artificial “organs” designed to replace the lungs’ gas exchange function by supplying oxygen and removing carbon dioxide (CO<sub>2</sub>) from blood. Full-flow venovenous ECMO (VV-ECMO), bicaval dual-lumen jugular VV-ECMO, and ECCO<sub>2</sub>R are modalities of ECLS for severe ARDS (Fig. 1). During full-flow VV-ECMO venous blood is typically withdrawn from the inferior vena cava through the femoral vein, and then reinserted into the jugular vein (V<sub>f</sub>-V<sub>j</sub>;

**Take-home message**

This review provides a summary of physiological concepts related to ECLS, as well as the rationale and evidence supporting the two main forms of ECLS for the treatment of ARDS: extracorporeal membrane oxygenation (ECMO) and extracorporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R). It also highlights evidence on complications, limitations, the ethical dilemmas in treating patients with ECLS and discusses future key research questions and challenges for this technology.

ECMO) or the contralateral femoral vein (V<sub>f</sub>-V<sub>f</sub> ECMO) after passing through the membrane oxygenator [6]. The high blood flow (commonly 4–8 L/min) and diffusion of gases between blood and the “sweep gas” flowing through the membrane lung’s fibers provide oxygen and remove carbon dioxide directly from blood, hence allowing lower intensity mechanical ventilation.

Bicaval, dual-lumen jugular VV-ECMO was initially considered promising given the single jugular cannulation. However, ECMO blood flow rates (Q<sub>ECMO</sub>) are limited by the diameter of the shared lumen for drainage, and its effectiveness is very dependent on optimal placement of the reinfusion port so that oxygenated blood is directed toward the tricuspid valve, limiting its use in some patients during the acute phase of ARDS. In a recent large international report, it was used in only 7% of patients as the primary ECLS approach [7].



**Fig. 1** Three different modalities of ECLS for acute respiratory distress syndrome. **A** Femoro-jugular venovenous extracorporeal membrane oxygenation (VV-ECMO) which enables full oxygenation and carbon dioxide removal in the acute phase of ARDS. Typical mechanical ventilation settings (EOLIA settings) aim to further protect the lung by reducing VT, RR, and ΔP; **B** Dual-lumen jugular VV-ECMO is an alternative cannulation strategy; **C** Extra-corporeal CO<sub>2</sub> removal, which may facilitate lung-protective ventilation by allowing a reduction of VT, Pplat, RR, ΔP and mechanical power (SUPERNOVA pilot settings) by ensuring partial carbon dioxide removal with marginal oxygenation in mild-to-moderate ARDS. VCV volume-controlled ventilation, PEEP positive end-expiratory pressure, VT tidal volume, Pplat plateau pressure, BIPAP/APRV biphasic positive airway pressure/airway pressure release ventilation, RR respiratory rate, ΔP driving pressure, Fr French, ARDS acute respiratory distress syndrome, ECLS extracorporeal life support, MV mechanical ventilation, FdO<sub>2</sub> fraction on oxygen in the sweep gas, MO, membrane oxygenator, Q<sub>ecmo</sub> (Q<sub>e</sub>) ECMO flow in L/min. Major changes between the three settings are highlighted in bold font. <sup>a</sup> Modified EOLIA settings with a set RR lower than in EOLIA. Decreasing respiratory rate (< 10–15 breaths/min) to reduce mechanical power seems desirable, although it may be achieved in most ARDS patients only with deep sedation and neuromuscular blockade

### Oxygenation

Understanding the physiological determinants of gas exchange is crucial for optimal application of ECMO. The oxygen content of blood is dependent on haemoglobin level, the partial pressure of oxygen ( $PO_2$ ), the oxygen-hemoglobin dissociation curve, and to a lesser extent, the dissolved oxygen. This has implications for the minimal blood flow required to provide full oxygenation (if required) [8], which is on the order of 4+ liters per minute.

The ability to oxygenate blood largely depends on the size and properties of the membrane oxygenator,  $Q_{ECMO}$ , and the difference in  $PO_2$  between the blood flowing into the oxygenator and the  $PO_2$  of the gas delivered to the membrane lung (sweep gas), typically oxygen or a blend of oxygen and air. The linear relationship between  $Q_{ECMO}$  and oxygen transfer favors the use of large drainage cannulas (23–29 Fr) to provide full oxygenation support. The drained venous blood oxygen saturation (i.e., pre-oxygenator oxygen saturation), is the second major component determining oxygen transfer during ECMO. It is affected by the recirculation (i.e. reinfused oxygenated blood which is withdrawn through the drainage cannula before it can circulate through the lung). Recirculation can be minimized either by femoral-jugular cannulation with a sufficient distance between the two tips of the cannulas, or using a properly positioned jugular dual-lumen cannula [9].

Because the (well-oxygenated) blood returned to the right atrium from the membrane oxygenator mixes with the remaining native venous return, an increase in cardiac output at constant ECMO flow rates will result in decreased systemic arterial oxygenation when native lung gas exchange is sufficiently impaired. In a physiological study performed in ten severe ARDS patients receiving  $V_F-V_j$  ECMO,  $Q_{ECMO}/\text{cardiac output ratio} \geq 60\%$  was associated with adequate blood oxygenation and oxygen delivery [8]. Other factors that affect systemic oxygenation include the complex interplay between intrapulmonary shunt, oxygen fraction to the native lung, oxygen fraction to the membrane lung, and total oxygen consumption [10].

### Carbon dioxide removal

At any given blood flow, carbon dioxide removal is more efficient than oxygenation. At physiological levels, the carbon dioxide content of a given volume of blood is substantially higher than the oxygen content, and thus, for a given ECMO flow rate a greater percent of the patient's  $CO_2$  production can be removed compared with the percentage of the oxygen consumption that can be provided [10, 11]. As well,  $CO_2$  is more soluble than  $O_2$ , allowing

it to diffuse across the membrane circuit with greater efficiency. To understand the performance of available ECCO<sub>2</sub>R devices, it is important to understand that  $CO_2$  removal will increase with increases in  $CO_2$  blood content, the partial pressure of venous  $CO_2$  ( $PvCO_2$ ), artificial lung surface area, as well as increases in sweep gas and blood flow through the membrane lung, although with ceiling effects for both. Blood flow rates of 1–3 L per minute (L/min) may be sufficient to fully remove the entire  $CO_2$  production of most patients, but insufficient to provide the patient's full  $O_2$  consumption. For a given membrane lung size and blood flow rate,  $CO_2$  removal will be increased with increasing sweep gas flow rate up to ~10–12 L/min [8]; a high  $PCO_2$  will increase the gradient for diffusion of  $CO_2$  out of the membrane; and artificial blood acidification can increase the amount of  $CO_2$  available to the membrane [12, 13].

### Rationale and potential indications of ECLS in patients with ARDS

Historically, ECMO was restricted to patients dying from refractory hypoxemia [10, 14]; however, recently it has become the standard of care in experienced ICUs for patients with very severe ARDS [15]. Beyond its ability to rescue patients with very severe gas exchange abnormalities not responding to standard treatment, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial strongly suggested that the main benefit of ECMO is through ameliorating ventilator-induced lung injury (VILI) [16]. Patients who were enrolled in the EOLIA trial due to severe respiratory acidosis (arterial  $pH < 7.25$  with  $PaCO_2 \geq 60$  mmHg for  $> 6$  h), rather than solely due to severe hypoxemia, appeared to benefit most [16], likely due to a reduction in ventilator-induced lung injury (VILI) secondary to decreased tidal volume (VT), respiratory rate (RR), plateau pressure (Pplat), driving pressure ( $\Delta P$ ), and mechanical power [7, 10, 17].

ECMO has a number of beneficial effects. Minimizing hypoxemia decreases tissue hypoxia, which may reduce organ dysfunction including neurocognitive sequelae [18]. ECMO decreases respiratory acidosis and right ventricular afterload and, therefore increase cardiac output [19]. Moreover, ECMO may reduce diaphragmatic myotrauma, by improving blood gases, hence decreasing respiratory drive. Keeping patients ambulatory when ECLS is used as a bridge to lung transplantation has been reported, but it is as yet unclear whether such a strategy is beneficial in ARDS patients [20]. If this strategy is applied, then close monitoring of respiratory drive [21] appears desirable to prevent additional lung injury due to patient respiratory effort [22].

Ideally, ECMO should be used in patients meeting EOLIA criteria (Tables 1 and 2) after proven conventional

**Table 1 Proposed indications and contraindications to ECMO for ARDS**

Indications	Relative contraindications	Absolute contraindications
EOLIA entry criteria <sup>a</sup> PaO <sub>2</sub> /FiO <sub>2</sub> < 50 mmHg for > 3 h PaO <sub>2</sub> /FiO <sub>2</sub> < 80 mmHg for > 6 h pH < 7.25 with a PaCO <sub>2</sub> ≥ 60 mmHg for > 6 h <sup>b</sup>	Invasive mechanical ventilation for more than 7–10 days Contraindication to anticoagulation Severe coagulopathy Advanced age Salvage ECMO (referred to as “rescue” in EOLIA), i.e., employing ECMO when severe right heart failure, or other severe decompensation occurs	Moribund state with established multiple organ failure Prolonged cardiac arrest Severe anoxic brain injury Massive intracranial hemorrhage Severe chronic respiratory failure with no possibility of lung transplantation Metastatic malignancy or hematological disease with poor short-term prognosis Other advanced comorbidities with poor short-term prognosis

<sup>a</sup> After proven conventional management (including lung protective mechanical ventilation, prone positioning and possibly neuromuscular blockade) for severe ARDS have been applied and failed. Less frequently, rescue ECMO may be deployed when a patient is too unstable for prone positioning, or when this is the only way to facilitate safe transport from a non-expert centre that is unable to apply evidence-based conventional practices

<sup>b</sup> With respiratory rate increased to 35 breaths per minute and mechanical ventilation settings adjusted to keep a plateau airway pressure of ≤ 32 cm of water

management (including lung protective mechanical ventilation [2] and prone positioning [23]) for severe ARDS have been applied and failed [15, 24]. Less frequently, rescue ECMO may be deployed when a patient is too unstable for prone positioning, or when this is the only way to facilitate safe transport from a non-expert centre that is unable to apply evidence-based conventional practices [15]. Lastly, employing ECMO when severe right heart failure, or other severe decompensation occurs, so-called salvage ECMO (referred to as “rescue” in EOLIA) should be avoided, where possible, as it is associated with higher mortality [16].

### Rationale and potential indications for ECCO<sub>2</sub>R in ARDS

When ECLS is applied at relatively low blood flow (e.g., 400–1000 mL/min) it can provide substantial CO<sub>2</sub> elimination (~20–70% of total CO<sub>2</sub> production), albeit with marginal improvement in oxygenation. Under these conditions, the technique is referred to as extra-corporeal CO<sub>2</sub> removal (ECCO<sub>2</sub>R). The rationale for using ECCO<sub>2</sub>R in ARDS is to facilitate lung-protective ventilation by allowing a reduction of VT, Pplat, RR, ΔP and mechanical power [25]; the extent of lung protection depends on the volume of CO<sub>2</sub> that can be removed by the device [26]. There is currently limited evidence to support the use of ECCO<sub>2</sub>R for ARDS outside the research setting [11, 27].

### Current evidence for the use of VV-ECMO in severe ARDS

First successfully deployed in a patient with ARDS in 1971, ECMO gained momentum due to two unrelated events in 2009: (1) the influenza A(H1N1) pandemic, in which national observational cohorts from France [28], Italy [29], United Kingdom (UK) [30], Australia and New Zealand [31], reported unexpected low mortality

(21–36%) in severely ill ARDS patients treated with ECMO; and, (2) publication in 2009 of the CESAR trial conducted in the UK [32], which evaluated a strategy of transfer to a single-center which had ECMO capability versus a strategy in which patients were treated conventionally at designated treatment centers (Table 2). The primary endpoint (composite of mortality or severe disability six months after randomization) was lower for the 90 patients randomized to the ECMO group (37% vs. 53%,  $p=0.03$ ). However, the study had numerous methodological issues. For example, many patients randomized to the ECMO arm did not receive ECMO (by design) and lung protective ventilation was not mandated in the control group.

The more recent multicenter, international EOLIA [16] trial has helped to define the role and safety of ECMO in managing severe ARDS, despite the fact that it was not “traditionally positive” [33]. Patients who fulfilled inclusion criteria (Table 2) were randomized to standard of care, including protocolized mechanical ventilation ( $n=125$ ), or to ECMO ( $n=124$ ) with protocolized reduction of ventilator pressures, volumes, and respiratory rates. Ninety percent of standard care patients and 66% of ECMO patients received a trial of prone positioning at some time during their course. Cross-over (i.e., receiving ECMO in the standard care group) was restricted to patients who were profoundly hypoxemic or hemodynamically unstable. The trial was stopped early for futility; there was a non-significant 11% absolute difference in 60-day mortality ( $p=0.087$ ). ECMO-treated patients had a significant reduction of cardiac failure, renal failure, and need for dialysis. There was a similar incidence of hemorrhagic stroke in the two groups.

Following the publication of EOLIA, Goligher et al. re-analysed the results of the trial using a Bayesian approach, [34] which demonstrated a high likelihood of a

Table 2 Main recent randomized controlled trials and a pilot study with ECLS for ARDS

Trial name/registration detailed	CESAR [ 23 ]	EOLIA [ 16 ]	XTRAVENT [ 17 ]	REST NCT02654327	SUPERNOVA Pilot [ 18 ]
Device	W-ECMO	W-ECMO	A-V ECCO <sub>2</sub> R	V-V ECCO <sub>2</sub> R	V-V ECCO <sub>2</sub> R
Status	Published	Published	Published	Stopped recruiting by DSMB	Published
Inclusion criteria/population	Severe ARDS 18–65 years Murray score > 3 or pH < 7.2 potentially reversible respiratory failure	Severe ARDS Ventilation ≤ 7 days PaO <sub>2</sub> /FiO <sub>2</sub> < 50 mmHg for > 3 h PaO <sub>2</sub> /FiO <sub>2</sub> < 80 mmHg for > 6 h pH < 7.25 with a PaCO <sub>2</sub> ≥ 60 mmHg for > 6 h, despite RR at 35/min	Moderate to severe ARDS Ventilation ≤ 7 days	Mechanically ventilated adult patients within 48 h of acute hypoxaemic respiratory failure (PaO <sub>2</sub> /FiO <sub>2</sub> < 150 mmHg) receiving at least PEEP of 5 cmH <sub>2</sub> O	Moderate ARDS expected ventilation duration > 24 h
Number of patients	180	249	79	1120 <sup>a</sup>	95
Interventional arm	consideration for treatment by ECMO in a referral centre	ECMO with FiO <sub>2</sub> 0.3–0.5; PEEP > 10 cmH <sub>2</sub> O, VT to obtain a Pplat ≤ 24 cmH <sub>2</sub> O, RR: 10–30/min	3 ml/kg ideal body weight and ECCO <sub>2</sub> R	W-ECCO <sub>2</sub> R to target VT ≤ 3 ml/kg and a Pplat ≤ 25 cmH <sub>2</sub> O	2-h run-in period followed by w-ECCO <sub>2</sub> R Reduction in VT (± RR) maintaining Pplat 23–25 cmH <sub>2</sub> O, and PaCO <sub>2</sub> at baseline (± 20%)
Comparator	conventional management	Ventilatory treatment according to the increased recruitment strategy from the Express trial Neuromuscular blocking agents, and prone positioning	conventional management (VT 6 ml/kg)	conventional management (VT 6 ml/kg)	Nil
Primary outcome	mortality or severe disability at 6 months	60-day mortality	28-day and 60-day VFD	90-day mortality	proportion of patients achieving ultra-protective ventilation with PaCO <sub>2</sub> not increasing more than 20% from baseline, and arterial pH > 7.30
Main findings	mortality or severe disability 6 months lower for the 90 patients randomized to the ECMO group (37% vs. 53%, <i>p</i> = 0.03), numerous methodological issues	ECMO is safe 60-day mortality - ECMO group (35%) - control group who did not cross over (41%) - cross over group (57%)	VFD within 60 days was not different between the study group and the control group In patients (PaO <sub>2</sub> /FiO <sub>2</sub> < 150) significant improved VFD in study patients compared to control	–	The proportion of patients who achieved ultra-protective settings by 8 h and 24 h was 78% and 82% Use of ECCO <sub>2</sub> R to facilitate ultra-protective ventilation was feasible

W-ECMO venovenous extracorporeal membrane oxygenation, A-V ECCO<sub>2</sub>R arteriovenous extracorporeal CO<sub>2</sub> removal, V-V ECCO<sub>2</sub>R venovenous extracorporeal CO<sub>2</sub> removal, DSMB data and safety monitoring board, ARDS acute respiratory distress syndrome, VFD ventilator-free day, PEEP positive end-expiratory pressure, VT tidal volume, Pplat plateau pressure, RR respiratory rate

<sup>a</sup> Initially planned before premature stop by the DSMB

survival benefit using ECMO, even when a strongly skeptical prior distribution was used. The individual patient data meta-analysis of CESAR and EOLIA included a total of 429 patients and showed that 90-day mortality was significantly lower in the VV-ECMO group compared with the control group (36% vs. 48%; relative risk, 0.75, 95% CI 0.60–0.94;  $p=0.013$ ;  $I^2=0\%$ ) [35]. Patients randomised to ECMO had more days alive out of the ICU and without respiratory, cardiovascular, renal and neurological failure.

The EOLIA trial [16], the post hoc Bayesian analysis [34], and systematic reviews and meta-analysis [35, 36] all consistently supported the use of venovenous ECMO in adults with severe ARDS treated in expert centers. As stated in the editorial addressing the Bayesian analysis, it is no longer a question of “Does ECMO work? because that question appears to be answered but by how much does ECMO work, in whom, and at what cost?” [37].

### ECMO during outbreaks of infectious diseases

ECMO has played an important role during previous respiratory viral outbreaks [31]. In a non-randomized study, transfer to an ECMO center was associated with lower hospital mortality compared with matched non-ECMO-referred patients [30]. Similarly, a retrospective chart review of 35 Middle East respiratory syndrome coronavirus (MERS-CoV) patients with refractory respiratory failure reported a lower in-hospital mortality rate in 17 patients who received ECMO compared with those who received conventional oxygen therapy [38]. Due to resource and human constraints, ECMO cannot easily be employed extensively in such outbreaks. Widespread application of proven conventional management approaches (i.e., protective mechanical ventilation, and prone positioning) before ECMO, and strict selection of patients most likely to benefit [39, 40] are all key since any health system could be rapidly overwhelmed if large numbers of patients require ECMO.

A recent study reported results on 83 patients under the age of 70 who fulfilled EOLIA trial criteria and received ECMO for very severe COVID-19-related ARDS [41]. Contrary to results early in the pandemic suggesting dismal outcomes for ECMO-treated COVID-19 patients [42], the estimated probability of death 60 days post-ECMO initiation was 31% (95% CI 22–42%) [41]. These results were similar to those from the EOLIA trial (35% at day 60) [16] and from the large prospective LIFEGARD registry (39% at day 180) [7]. A large ( $n=1035$ ) registry study of ECMO for COVID-19 involving predominantly respiratory failure, yielded an estimated cumulative incidence of in-hospital mortality of 37.4% (95% CI 34.4–40.4) at 90 days after initiation of ECMO, offering provisional support for the use of

ECMO in highly selected patients with COVID-19 [43]. A very recent study identified a subgroup of patients with COVID-19-related ARDS characterised by low static compliance of the respiratory system and high D-dimer concentration that have a markedly increased mortality compared with other patients (56% vs. 28%) [44]. These patients may potentially be considered for wider use of ECMO.

### ECCO<sub>2</sub>R in the context of mild-to-moderate ARDS

Investigation of the potential benefits of ultra-protective ventilation [45] have led to renewed interest in ECCO<sub>2</sub>R. The technique has markedly improved in recent years [11], using more biocompatible circuits [10, 46], dual-lumen heparin-coated catheters with a diameter closer to dialysis catheters than to ECMO cannulas [47], and ultrasonography-guided catheter insertion.

ECCO<sub>2</sub>R allows for a reduction in VT, Pplat,  $\Delta P$  [48], mean minute ventilation [49], and therefore enhances protective or ultra-protective ventilation [50]. An increase in positive end-expiratory pressure (PEEP) to counteract derecruitment, induced by the tidal volume reduction [51], appears desirable. In this context, ECCO<sub>2</sub>R may be associated with a significant reduction of systemic and pulmonary inflammatory mediators [49]. The strategy of ultraprotective lung ventilation with extracorporeal CO<sub>2</sub> removal (SUPERNOVA) pilot study included 95 patients with moderate-to-severe ARDS in 23 ICUs. ECCO<sub>2</sub>R allowed a significant decrease in mechanical power with reductions of Pplat (27 to 24 cmH<sub>2</sub>O), VT (6 to 4 mL/kg), RR (28 to 24 breaths/min), and minute ventilation (10 to 6 L/min) [51]. Despite the significant reduction of minute ventilation, pH was maintained  $>7.3$ , and the increase in PaCO<sub>2</sub> was  $<20\%$  from baseline. However, this strategy may not benefit all patients equally [48, 52], as the lung-protective benefits of ECCO<sub>2</sub>R increase with higher alveolar dead space fraction, lower respiratory system compliance, and higher device performance [25]. Therefore, these patients [52] should preferentially be enrolled in randomized controlled trials, and worsening hypoxemia, reported in up to 40% of patients [53] should be addressed. The hypoxemia can be secondary to a decreased mean airway pressure, and a lower ventilation-perfusion ratio, or due to a lower partial pressure of alveolar oxygen due to a decreased lung respiratory quotient and hypoventilation in the native lung [54].

The CO<sub>2</sub> removal performance and device-related adverse events differ across available ECCO<sub>2</sub>R devices [26]. The SUPERNOVA pilot study used three different devices [45]. A lower incidence of membrane clotting was reported with two higher flow (800–1000 mL/min) devices (14%), with significantly higher rates of adverse

events with the low blood flow device (300–500 mL/min), despite similar anticoagulation regimens [26, 51].

Although theoretically very appealing, the impact on outcomes of a strategy combining ultra-protective ventilation and ECCO<sub>2</sub>R is unknown, as only physiological proof-of-concept and feasibility studies are available; randomized controlled trials are ongoing (Table 2). Interestingly, the XTRAVENT study, which used a pumpless arterio-venous ECCO<sub>2</sub>R device in moderate ARDS, observed similar mortality between the intervention group (40 patients ventilated with 3 mL/kg predicted body weight (PBW) and ECCO<sub>2</sub>R) and the control group (39 patients ventilated with 6 mL/kg PBW) [48]. Of note, in a post hoc analysis, the treated subgroup with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) < 150 mmHg achieved earlier weaning than the controls.

### Specific management during VV-ECMO

The main goals of ECMO are to provide adequate gas exchanges while minimizing VILI. In the acute phase of ARDS, using a large venous drainage cannula—a prerequisite for high  $Q_{\text{ECMO}}$  (> 4 L/min)—enables adequate oxygenation while applying “ultra-protective lung ventilation.” How much the intensity of mechanical ventilation should be decreased, and whether or not we should maintain the lungs open to avoid complete lung collapse, are still a matter of debate [55, 56]. Some degree of ventilation, while maintaining  $\text{PEEP} \geq 10$  cmH<sub>2</sub>O, during ECMO improved survival in a retrospective study [57]. On the other hand, a larger reduction in mechanical ventilation intensity through lower driving pressure [58] was associated with lower mortality and near-apneic ventilation resulted in fewer histological lesions of lung injury in an animal model [59]. Similarly, decreasing respiratory rate (< 10–15 breaths/min) to reduce mechanical power seems desirable [49, 50], although it may be achieved in most ARDS patients only with deep sedation and neuromuscular blockade. This strategy may be less appropriate as the patients’ course progresses as it may delay physical and cognitive rehabilitation. Future trials should assess these strategies in severe ARDS patients during ECMO.

Several techniques have been used to optimize lung recruitment while minimizing lung injury during ECMO. First, individualization of PEEP during ECMO using transpulmonary pressure measurements [60] or electrical impedance tomography (EIT) [61] appear promising. Second, some centers currently perform prone positioning during ECMO with a goal of reducing VILI [41, 62]. Two recent retrospective series of severe ARDS patients showed that prone positioning, while on-ECMO demonstrated higher ECMO-weaning and survival rates [62, 63]. However, randomized controlled trials of

prone positioning during ECMO are needed before recommending this practice routinely. Lastly, the use of pressure-controlled ventilation [7] may allow for easy detection of patient recovery by observing increases in VT during ECMO.

When the patient is stabilized, preventing diaphragm atrophy by introducing spontaneous breathing activity may be desirable. However, even during this rehabilitation phase of severe ARDS, the respiratory drive of the patient may still be (too) high, which may be controlled by increasing sweep gas flow which lowers  $\text{PaCO}_2$  [22]; the efficacy of this maneuver may be assessed by measurement of patient effort and work of breathing. Ventilation strategies on ECMO integrating respiratory drive monitoring deserve investigation. Patients receiving ECMO may also benefit from less sedation and early rehabilitation, and retrospective studies have found that rehabilitation, including mobilization, during ECMO was feasible and safe, even in patients with very high severity of illness [20, 64].

In some circumstances, severe hypoxemia persists under VV-ECMO. This situation requires a multi-step approach [65] that should begin with a complete circuit check, followed by ensuring adequate positioning of cannulas to minimize blood recirculation and optimize the ratio of ECMO blood flow to cardiac output. Moderate hypothermia to decrease tissue oxygen utilization (with a depressant effect on cardiac output). Short-acting beta-blockers have been used for refractory hypoxemia to decrease the extracorporeal blood flow-to-systemic blood flow ratio ( $Q_{\text{E}}:Q_{\text{S}}$ ) [10], which will improve arterial oxygenation but will simultaneously decrease cardiac output, and therefore will have an overall variable effect on tissue oxygen delivery and so should be approached with caution if oxygen delivery is not directly measured, especially given the very limited data supporting this approach. Packed red blood cells may be transfused with the idea of maximizing oxygen delivery. However, the optimal transfusion threshold for these patients has not been established and transfusion is associated with adverse outcomes in the setting of ARDS [65]. Prone positioning (PP) during ECMO may also be effective by increasing the proportion of poorly-aerated areas in dependent lung regions [62]. Further data are needed to better understand the risk-to-benefit ratio of this intervention.

ECMO weaning, which is typically performed before weaning from mechanical ventilation [7], should be tested when native lung function has sufficiently recovered allowing adequate oxygenation and safe (or protective) mechanical ventilation settings (e.g., ventilator  $\text{FiO}_2 \leq 60\%$ , sweep gas flow < 8 L/min, and  $\text{VT} \geq 4.5$  mL/kg PBW with  $\text{Pplat} \leq 24$  cmH<sub>2</sub>O or  $\Delta\text{P} \leq 14$  cmH<sub>2</sub>O) and involves regular trials with the sweep gas turned off. A

detailed ECMO weaning algorithm is proposed in Fig. 2. Based on EOLIA, current weaning success criteria for safe decannulation from ECMO [16] are:  $PaO_2 \geq 60$  mmHg,  $SaO_2 \geq 90\%$ , with  $FiO_2 \leq 60\%$ ;  $PaCO_2 \leq 50$  mmHg or  $pH \geq 7.36$ , with respiratory rate  $\leq 28$ /min;  $P_{plat} \leq 28$  cmH<sub>2</sub>O; and no signs of acute cor pulmonale.

Modern management of VV-ECMO with heparin-coated surfaces and high  $Q_{ECMO}$  have allowed for a

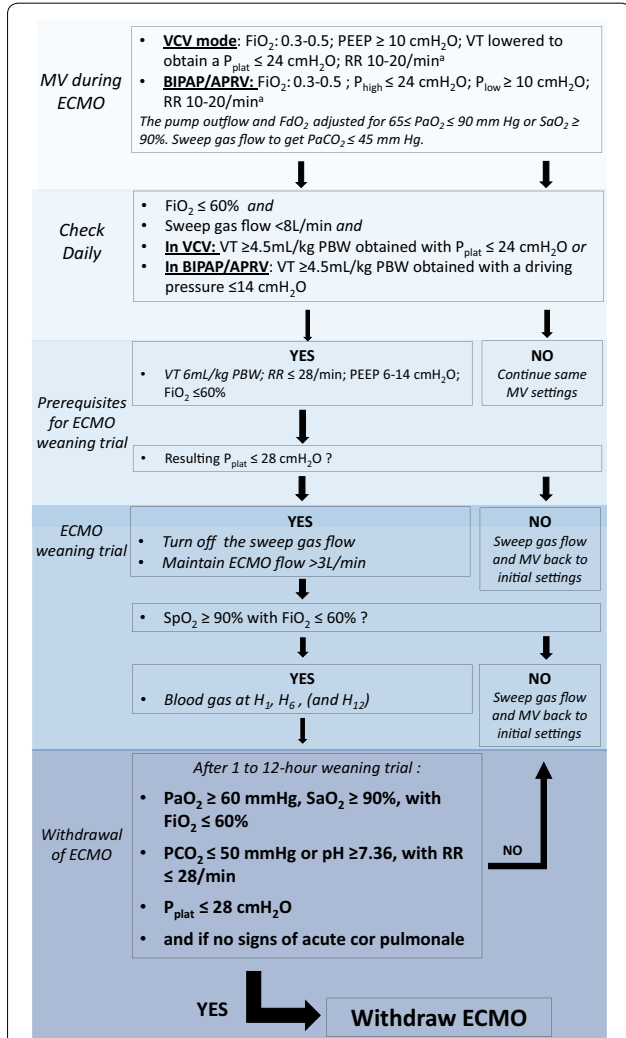
substantial decrease in systemic anticoagulation [66]. Unfractionated heparin (target aPTT 40–55 s) or anti-Xa activity (0.2–0.3 IU/mL) are commonly used [16]. However, these may need to be revised upwards in high inflammatory syndromes or infections associated with vascular injury, such as COVID-19-related ARDS, although the data on this are not clear [41].

Close daily monitoring to reduce ECLS-related complications is mandatory, and requires intensive education and training (Fig. 3). Although relatively infrequent in the EOLIA trial [16], intracranial hemorrhage is associated with poor outcomes. The rapidity with which CO<sub>2</sub> is reduced after ECLS initiation has been implicated in development of neurological complications and the sweep gas flow through the oxygenator should be adjusted to avoid a drop in  $PaCO_2 > 20$  mm Hg/h over the first 24-h of ECMO in most patients [67, 68]. Similarly, interactions between the blood, the pump, and the artificial surfaces of the circuit and membrane generate blood trauma and activate coagulation and fibrinolysis pathways associated with increased inflammatory responses. Daily monitoring of platelet count, fibrinogen, anticoagulation levels and other parameters are aimed at recognizing the onset of complications such as clotting, bleeding and hemolysis, and the need to change portions of the circuit. In addition, thrombosis and hemolysis appear to be more frequent with low-flow ECMO or ECCO<sub>2</sub>R. The clotting risk is directly related to the type of device, the extracorporeal blood flow, and the size of the cannulas [26]. Lastly, the ECLS population may be particularly susceptible to nosocomial infections because of concomitant critical illness, indwelling catheters, and prolonged hospitalization. Management of infections during ECLS is more challenging due to alterations in pharmacokinetics of antimicrobial agents in the presence of an extracorporeal circuit [69].

**ECMO activity organization, long-term outcomes, and ethical questions**

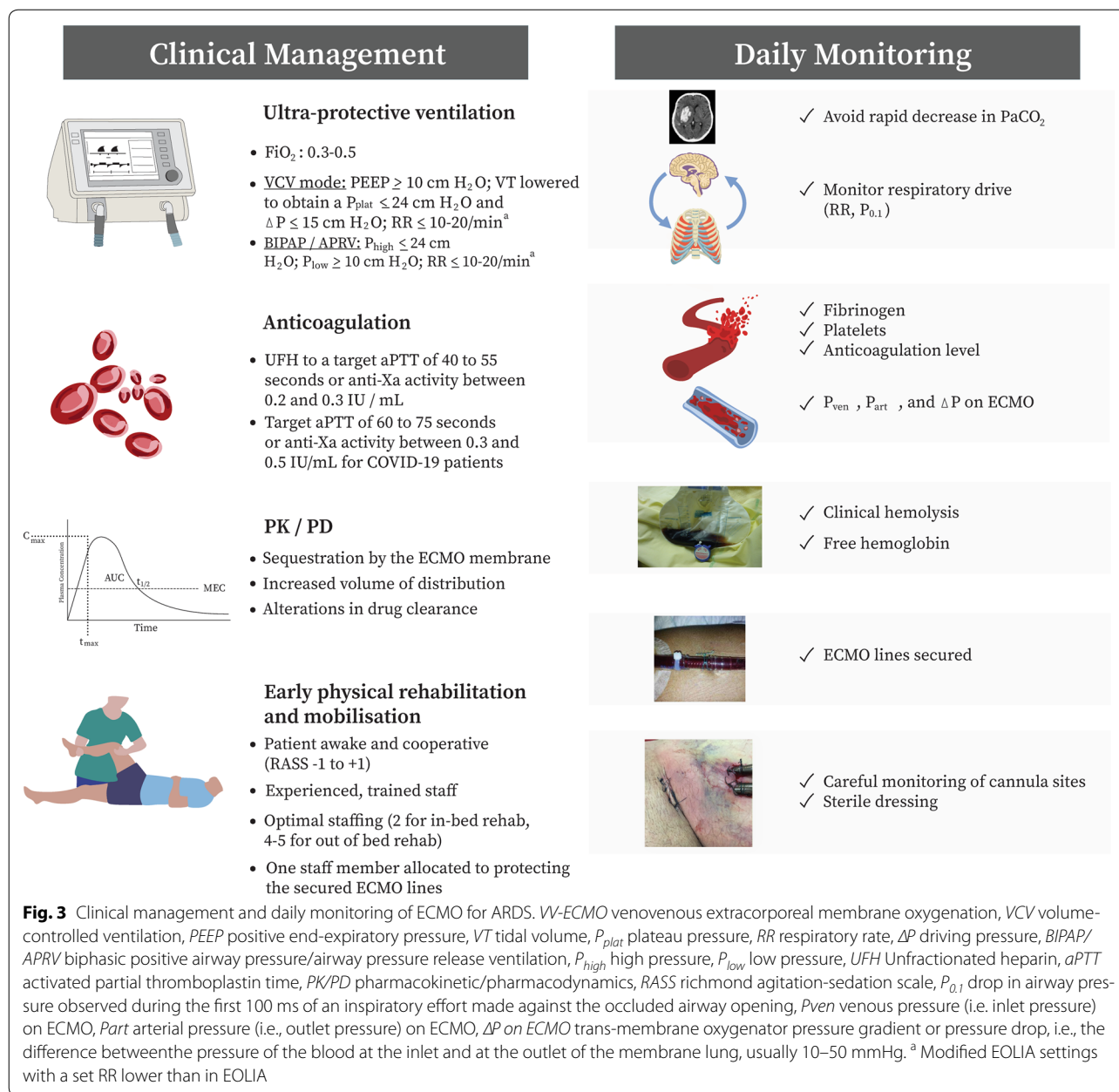
An analysis of the international ELSO Registry reported an association between higher annual ECMO volume and lower case-mix—adjusted mortality for ECMO-treated neonates and adults [70] A position paper [71] by an international group of experts advocated for a regional and inter-regional ECMO network of hospitals around an ECMO referral center with a mobile ECMO unit to retrieve the most severe patients.

Patients supported with ECMO generally have prolonged ICU and hospital lengths of stay [16, 40, 72], which likely contribute to worse pulmonary function, quality of life, and psychological status. However, the long-term prognosis after ECMO for ARDS has been insufficiently evaluated. Patients in the ECMO arm of



**Fig. 2** VV-ECMO weaning algorithm in severe acute respiratory distress syndrome. VV-ECMO venovenous extracorporeal membrane oxygenation, VCV volume-controlled ventilation, PEEP positive end-expiratory pressure, VT tidal volume,  $P_{plat}$  plateau pressure, BIPAP/APRV biphasic positive airway pressure/airway pressure release ventilation,  $P_{high}$  high pressure,  $P_{low}$  low pressure, RR respiratory rate, MV mechanical ventilation,  $F_iO_2$  fraction on oxygen in the sweep gas, PBW predicted body weight, H hour. <sup>a</sup> Modified EOLIA settings with a set RR lower than in EOLIA. Decreasing respiratory rate (< 10–15 breaths/min) to reduce mechanical power seems desirable, although it may be achieved in most ARDS patients only with deep sedation and neuromuscular blockade





the CESAR trial [32], and 12 influenza A(H1N1) ECMO-treated patients [73] had comparable or better health-related quality of life compared with those ARDS patients treated with conventional management. Eighty-four six-month survivors reported persistent physical and emotional-related difficulties, with anxiety, depression, or post-traumatic stress syndrome symptoms reported, by 34, 25 and 16% respectively [40].

Venovenous ECMO can be associated with complex ethical dilemmas, particularly in situations where patients are unlikely to recover sufficiently to transition to conventional mechanical ventilation, and are

not candidates for lung transplantation [74]. In these circumstances, criteria regarding continuation or withdrawal of ECMO are not strictly established and may differ among caregivers, ECMO centers, and countries. In a recent survey of 539 physicians from 39 countries across 6 continents, these decisions were strongly influenced by whether a patient's or surrogate's wishes were known, the level of consciousness of the patient, and perceived "futility" of the clinical situation [75]. Weighing the potential benefits and risks of ECMO using predictive survival models [39, 40], and improving doctor-patient/surrogate communication surrounding the benefits and limitations

of ECMO before its initiation are crucial. Shared decision-making with patients and family regarding end-of-life decisions on ECMO are recommended [75].

### Challenges for the future: research agenda

The EOLIA trial took 5.5 years to enroll 249 patients. Given the logistical hurdles, a new randomized controlled trial comparing ECMO versus conventional mechanical ventilation management seems highly unlikely. The major question now is rather: “How to provide better ECMO care?”

The management of mechanical ventilation during ECMO warrants further investigation. Studies are needed to investigate the impact of strategies such as larger reductions in mechanical ventilation intensity, frequent use of prone positioning, close control of respiratory drive, and ECMO without invasive mechanical ventilation. More work is needed to decrease the burden of ECMO-induced coagulopathy and associated bleeding, which is particularly important for ECCO<sub>2</sub>R. This includes work on improved biocompatible materials to reduce hemorrhagic or thrombotic adverse events; on pump technology to minimize shear stress, and hemolysis especially at low flows [76]. Beyond safety, the degree of benefit of ultra-protective ventilation remains to be proven [77] and large clinical trials to investigate the impact of ECCO<sub>2</sub>R for ARDS on outcomes are urgently needed (Table 2). Moreover, future research should focus on the selection of patients who will most likely benefit from the use of extracorporeal support [52, 78]. Importantly, research networks, such as the International ECMO Network (ECMONet; [www.internationalecmonet.org](http://www.internationalecmonet.org)), and large ECMO registries, such as the registry of the Extracorporeal Life Support Organization (ELSO; [www.elseo.org](http://www.elseo.org)), will be critical to achieving these future research aims.

### Conclusion

Although VV-ECMO is now a safe and viable strategy for severe ARDS when performed in experienced centers, it should not be a substitute for proven conventional ARDS management. Therefore, the initial management of patients with severe ARDS should always include lung protective ventilation and prone positioning, unless contraindicated or not technically feasible [79]. Future efforts in the field should focus on the improvement of ECMO care and elucidation of ECCO<sub>2</sub>R on patient-centred outcomes [80].

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### Acknowledgements

We thank Savannah Soenen for the creation of the figures.

### Author contributions

Drafting of the manuscript: C, S, S, B. Critical revision of the manuscript for important intellectual content: all authors.

### Compliance with ethical standards

### Conflicts of interest

AC reports grants from Getinge, personal fees from Getinge, Baxter and Xenios outside the submitted work. AC is also the recent past president of the EuroELSO organization and a member of the executive and scientific committees for ECMONet. MS reported personal fees from Getinge, Drager, and Xenios, outside the submitted work. MS is also member of the Data Committee for ECMONet. CH is a member of the steering and scientific committees for ECMONet. EF reports personal fees from ALung Technologies, Fresenius Medical Care, Getinge, and MC3 Cardiopulmonary outside the submitted work. NF reports consulting fees from Getinge and Xenios. NF is a member of the executive and scientific committees for ECMONet. JF is current president of Asia Pacific ELSO, Exec of ECMONet, and has received grant funding from Getinge, Xenios, Drager and CSL. He is co-founder of BiVACOR (mechanical support device). He declares no personal fees. SJ reports receiving consulting fees from Drager, Fresenius-Xenios, Baxter, Medtronic, and Fisher & Paykel. AP reports personal fees for consulting/lectures from Maquet, Xenios, Baxter, and Boehringer Ingelheim. AS is on the medical advisory boards for Baxter and Xenios. Hs is Chair of the Scientific Committee of the International ECMO Network (ECMONet). DB receives research support from ALung Technologies. He has been on the medical advisory boards for Baxter, Abiomed, Xenios and Hemovent. DB is also the President-elect of the Extracorporeal Life Support Organization (ELSO) and the Chair of the Executive Committee of the International ECMO Network (ECMONet). The other authors declare that they have no conflicts of interest related to the purpose of this manuscript.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 22 September 2020 Accepted: 10 October 2020

Published online: 2 November 2020

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