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Extracorporeal carbon dioxide removal for acute respiratory failure: a review of potential indications, clinical practice and open research questions

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Abstract

Extracorporeal carbon dioxide removal (ECCO₂R) is a form of extracorporeal life support (ECLS) largely aimed at removing carbon dioxide in patients with acute hypoxemic or acute hypercapnic respiratory failure, so as to minimize respiratory acidosis, allowing more lung protective ventilatory settings which should decrease ventilator-induced lung injury. ECCO₂R is increasingly being used despite the lack of high-quality evidence, while complications associated with the technique remain an issue of concern. This review explains the physiological basis underlying the use of ECCO₂R, reviews the evidence regarding indications and contraindications, patient management and complications, and addresses organizational and ethical considerations. The indications and the risk-to-benefit ratio of this technique should now be carefully evaluated using structured national or international registries and large randomized trials.

Keywords: Acute respiratory failure, Extracorporeal carbon dioxide removal, Mechanical ventilation, Outcome

Introduction

Extracorporeal carbon dioxide removal (ECCO₂R) is a form of extracorporeal life support (ECLS) [1] aimed at removing carbon dioxide via an extracorporeal circuit to help manage acute respiratory failure [2–4]. To date, there is a paucity of scientific evidence to support its widespread use [3–5], while complications associated with the technique remain concerning [4, 6–8].

This review explains the physiological basis underlying the use of ECCO₂R, reviews the evidence informing indications, contraindications, patient management, and complications; addresses organizational considerations; and highlights the need for further research.

What is ECCO₂R?

Definition

ECLS is an approach in which oxygen (O₂) is added and carbon dioxide (CO₂) removed from blood that has been pumped from a patient through a device functioning as an artificial lung (typically referred to as a membrane lung or oxygenator). An international consensus statement clarified the nomenclature for extracorporeal support [1] as follows: ECLS is the overarching term to describe gas exchange techniques that take place extracorporeally. ECLS comprises extracorporeal membrane

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oxygenation (ECMO), which provides both full oxygenation and CO₂ removal, and extracorporeal CO₂ removal (ECCO₂R). ECCO₂R systems differ from traditional ECMO setups in several ways [2, 3, 9]. ECCO₂R is the term used to define the subset of ECLS in which lower extracorporeal blood flow rates (~200–1500 mL/min) are used to remove CO₂ [4, 5, 10], since the blood flow rates needed to reduce hypercapnia are much lower than required to achieve adequate oxygenation in hypoxemic patients [2]. By contrast, ECMO describes ECLS at blood flow rates sufficiently high (typically >2.5 L/min) to provide a meaningful percentage of a patient's O₂ requirements [2, 11].

Although the flow rates used during ECCO₂R are insufficient to fully oxygenate the blood of an adult, some oxygen will be added to the blood, if oxygen is a component of the fresh gas flow. Thus, the term ECCO₂R is in some ways a misnomer. Although in the literature ECCO₂R is often defined based on the flow rate through the extracorporeal circuit, this approach is not entirely correct. As such, we suggest ECCO₂R is best defined based on the clinician's intended use [2]. For example, if the goal of the clinician in applying ECLS is to remove CO₂, then the technique is ECCO₂R, irrespective of the blood flow rate. If the goal is to improve oxygenation, then the technique is ECMO. If the goal is to address both O₂ and CO₂, then the convention is to use the term ECMO (even though ECMO-ECCO₂R might in theory be more accurate), since flow rates that provide adequate oxygenation, also remove large volumes of carbon dioxide.

Physiological rationale

Because of differences between O₂ and CO₂ with respect to the shape of their disassociation curves, gas diffusivity, and most importantly, gas carrying capacity of blood, the volume of blood that has to be directed through the artificial lung to provide adequate oxygenation versus adequate removal of CO₂ varies substantially. One liter of blood with a partial pressure of arterial carbon dioxide (PaCO₂) of 40 mmHg contains ~500 mL of CO₂. Thus, theoretically a maximally efficient ECLS circuit at a blood flow of 1 l/min could easily remove an "average" patient's full CO₂ production (~250–300 mL/min). This represents the physiological rationale underlying the use of ECCO₂R; by removing some or all of a patient's CO₂ production, less CO₂ must be removed via the patient's lungs. Thus, ECCO₂R can be used to decrease the intensity of ventilation, thereby minimizing ventilator-induced lung injury, and/or decreasing the work of breathing, even when the CO₂ removed is less than the full CO₂ production [12]. Conversely, the same 1 L/min blood flow rate can only add ~40 mL/min of oxygen, substantially less than the metabolic O₂ consumption of ~200 mL/

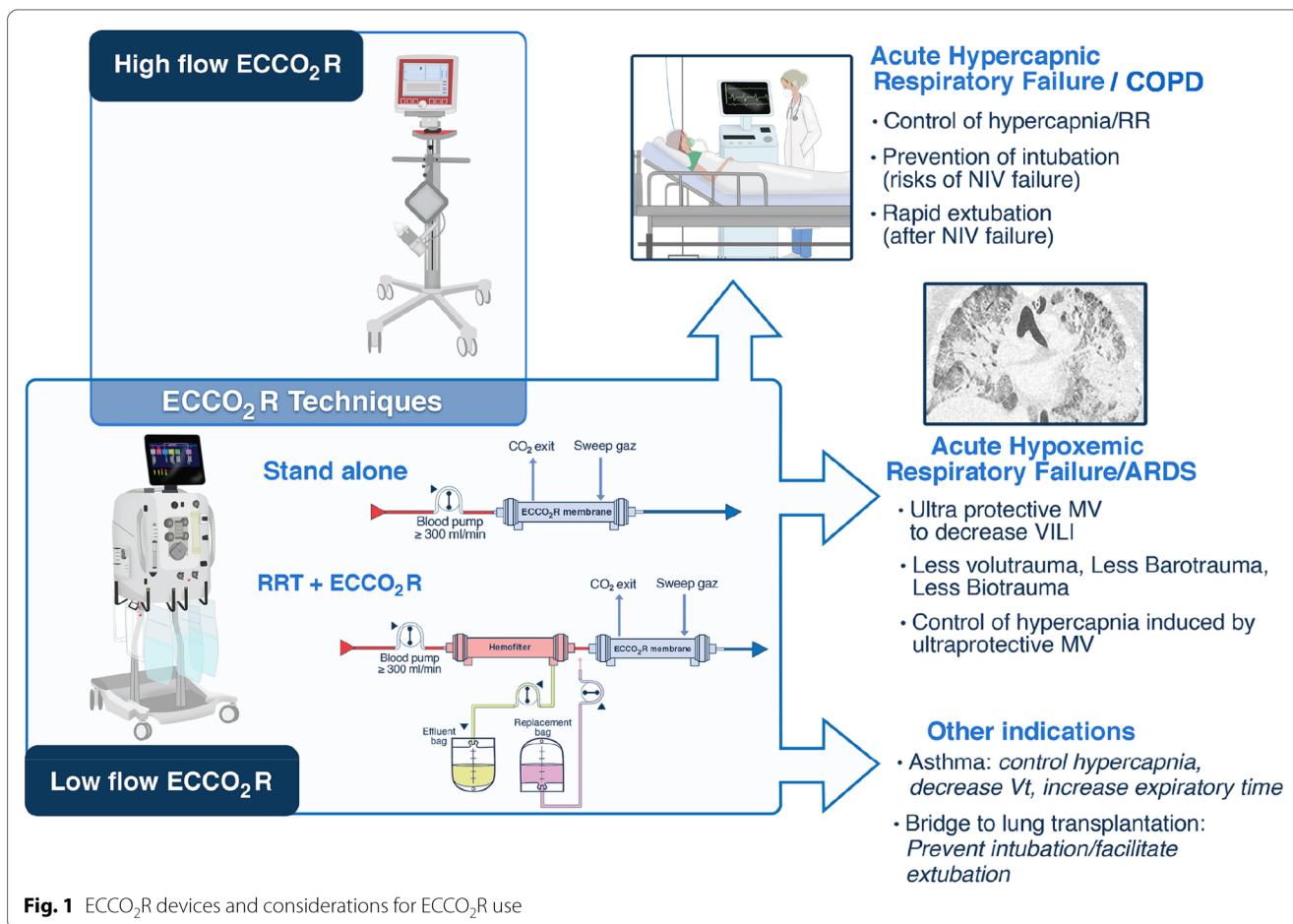
ECCO₂R has been increasingly used in patients with respiratory failure, despite the lack of high-quality evidence and the negative results of a recent randomized trial in patients with acute hypoxemic respiratory failure. The indications and the risk-to-benefit ratio of this technique should now be carefully evaluated using structured national or international registries and large randomized trials.

min, and thus would be insufficient to provide the entire metabolic oxygen requirements.

Types of ECCO₂R, machines, material and configurations

Historically, arterio-venous pumpless devices were used, which drive blood flow across the extracting membrane using the patient's native arterio-venous blood pressure gradient. However, due to vascular complications (bleeding, ischemia, compartment syndrome, pseudoaneurysm) the arteriovenous ECCO₂R technique has faded from clinical practice in recent years [13]. Currently ECCO₂R devices are most often characterized by the use of smaller catheters than used during ECMO, ranging in caliber from 13 to 18 Fr and usually placed in a veno-venous configuration using the Seldinger technique under ultrasound or fluoroscopic guidance (Fig. 1). For some systems, the use of a double-lumen cannula inserted into a central vein is preferred, enabling a blood flow of about 1 L/min [4, 14], depending on the size of the catheter.

The blood flow through the ECCO₂R device is usually driven by a magnetic roller (continuous or peristaltic) pump, or by centrifugal rotor, aimed at minimizing heat and mechanical trauma to the blood cells. The surface area of the membranes, mostly composed of poly-4-methyl-1-pentene (PMP), often range between 0.3 and 1.8 m² (Fig. 1) [2, 4, 8, 9, 15, 16]. The purge volume ranges between 140 and 250 mL, and blood flow ranges between 0.2 and 1.5 L/min. When blood flow is <500 mL/min, CO₂ elimination through the device will be about 20–40% of the patient's CO₂ production (VCO₂), depending on the size and properties of the membrane lung, the PaCO₂ gradient for CO₂ diffusion across the membrane, and the patient's VCO₂. An innovative approach to increase the CO₂ elimination at any fixed flow rate has been developed by Zanella and colleagues [17]. With this technique called "respiratory electro dialysis", blood is regionally acidified using an electro dialysis cell, bicarbonate is exchanged with chloride, leading to an increase in PCO₂ before the blood enters the membrane lung, nearly doubling CO₂ extraction. Other techniques such as the addition of carbonic anhydrase to the membrane [18] or regional acidification of extracorporeal blood by means of an ion-exchange resin [19] have been explored



as approaches for extracting more CO₂ as blood passes through the membrane lung.

ECCO₂R can be integrated into standard continuous renal replacement therapy (CRRT) circuits (ECCO₂R-CRRT) [20], providing both CO₂ removal and hemofiltration/dialysis in cases where there is concomitant acute kidney injury (Fig. 1). The blood with carbon dioxide removed (with some oxygen added as well) is returned to the right heart for systemic distribution.

Potential indications for ECCO₂R

Acute hypoxemic respiratory failure

The concept of using ECCO₂R to decrease the intensity of mechanical ventilation and associated ventilator-induced lung injury in acute hypoxemic respiratory failure patients is not new [12]. Lowering tidal volume (V_t), driving pressure (i.e. end-inspiratory plateau pressure minus positive end-expiratory pressure: ΔP) and respiratory rate (RR) can reduce the mechanical power (Power_{RS}, i.e. the energy transmitted to the lungs by the mechanical ventilator). This strategy that decreases pulmonary stress and strain, can decrease ventilator-induced lung injury and

may improve survival [21–23]. An initial small (n=40) randomized clinical trial investigating ECCO₂R was conducted over 25 years ago in patients with acute distress respiratory syndrome (ARDS) [24]. Although mortality was not significantly different between groups, it was numerically higher in patients receiving ECCO₂R, limiting enthusiasm for its use for many years. These initial reports used modified ECMO technology rather than dedicated ECCO₂R devices and experienced technical difficulties. Over the years, there have been major technological advances in the equipment used to provide ECMO [2]. As well, using this improved equipment, there has been emerging data supporting the use of ECMO for severe ARDS [11, 25–27]. This has led to improvements in ECCO₂R devices, and an increased interest in the role of ECCO₂R in acute hypoxemic respiratory failure, particularly to limit injurious ventilation, which may occur even in patients receiving conventional lung protective ventilation [28]. Indeed, the safe threshold for volume- and pressure-limited ventilation remains uncertain and data suggest further reduction in volumes and pressures below

what is regarded as conventional lung protective ventilation might be associated with better outcomes [29].

In patients with ARDS (Table 1), ECCO₂R to facilitate the use of lower tidal volumes [$\sim 3\text{--}4$ mL/kg predicted body weight (PBW)] reduced pulmonary inflammation, suggesting reduced ventilator-induced lung injury could be achieved with this approach [30]. A systematic review of ECCO₂R in patients with acute respiratory failure concluded that ECCO₂R facilitated the use of lower tidal volume ventilation; however, there was a paucity of high-quality data to demonstrate an effect on clinical outcomes. In addition, complication rates varied greatly across the studies included [31]. A post hoc analysis of the Xtravent study found that in the patients with greater hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 150$ mmHg), ECCO₂R was associated with more ventilator-free days at 60 days [13]. The SUPERNOVA pilot trial investigated feasibility and safety of three different ECCO₂R systems in patients with ARDS ($n=95$). Use of ECCO₂R allowed a reduction in tidal volume from approximately 6 to 4 mL/kg PBW and a statistically significant decrease in ΔP from 13 to 9 cmH₂O, with minimal change in PaCO₂. Overall, serious adverse events were infrequent [4].

The recently completed REST trial was a multicenter clinical trial conducted in the United Kingdom (UK), which recruited 412 adult patients receiving mechanical ventilation for acute hypoxemic respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg) [5]. Patients were randomized to receive lower than standard tidal volume ventilation facilitated by ECCO₂R, or to conventional low tidal volume ventilation. The trial was stopped early because of futility and feasibility. There was no difference in the primary outcome of 90-day mortality in the ECCO₂R group compared to the standard care group (41.5 vs 39.5% respectively; $p=0.68$). There were significantly fewer ventilator-free days in the ECCO₂R group. Serious adverse events were reported more commonly in the ECCO₂R group, the majority related to bleeding complications including intracranial hemorrhage. Many limitations of the REST trial have been underlined. At randomization, ARDS was present in only 60% of the patients, ΔP was < 15 mmHg in 50% and despite marked hypoxemia (median $\text{PaO}_2/\text{FiO}_2$, 118 mmHg), the median positive end-expiratory pressure (PEEP, 10 cmH₂O) was lower than in other ARDS trials with similar patients and only 11% of the patients had been proned. On day 2 post-randomization, the decrease in V_t (6.3–4.5 mL/kg) and in ΔP (15–12 cmH₂O) from baseline were modest, while increase in the respiratory rate (from 24 to 27/min) and in PaCO₂ (from 54 to 61 mmHg) were observed. These data suggest that the device used in this study may have provided insufficient CO₂ removal to reach ultraprojective ventilation while controlling respiratory acidosis. It should also be noted that most of the sites were naïve

to the intervention before the study commenced. On the basis of these data, the use of this technology of low-flow ECCO₂R to facilitate lower tidal volume ventilation cannot be recommended in this population [5]. Future trials of ECCO₂R in acute hypoxemic respiratory failure should consider devices providing higher CO₂ removal, allowing greater reduction in the intensity of mechanical ventilation with adequate control of respiratory acidosis, and should take advantage of other clinical and physiologic characteristics to enrich the study population, although this approach remains unproven [32].

Acute hypercapnic respiratory failure in the setting of chronic obstructive pulmonary disease

In patients with acute hypercapnic respiratory failure (Table 2), the prognosis worsens when intubation or prolonged invasive ventilation is required [33]. In this context, ECCO₂R may be used to prevent intubation (Table 2). In a multicenter, retrospective, case-controlled study including 42 patients with acute hypercapnic ventilatory failure not responding to non-invasive ventilation (NIV), 90% of those who received ECCO₂R with the pumpless arteriovenous technique did not require intubation. Compared to the matched control group, there was a trend toward a shorter hospital length of stay in the ECCO₂R group ($p=0.056$), while short- and long-term survivals were similar [34]. In a prospective study, 25 patients with acute hypercapnic respiratory failure refractory to NIV were treated with a veno-venous ECCO₂R system [14]. Endotracheal intubation was avoided in 56% of patients in the ECCO₂R group with a mean extracorporeal blood flow of 1.3 L/min. However, 36% of patients suffered major bleeding complications. In comparison with a matched historical control there were no significant differences in length of stay or mortality [14]. Similar results were reported by Del Sorbo et al. in a series of 25 chronic obstructive pulmonary disease (COPD) patients at risk of NIV failure [7].

Alternatively, ECCO₂R may be used to facilitate or accelerate weaning in those who needed urgent mechanical ventilation (Table 2). In a pilot study, five subjects with COPD exacerbations with uncompensated hypercapnia requiring invasive mechanical ventilation (IMV) were enrolled in a prospective, feasibility trial using ECCO₂R [35]. Endotracheal extubation occurred in all patients within 24 h of ECCO₂R initiation and all patients were able to perform active physical rehabilitation during ECCO₂R support. All of these patients survived until discharge from the hospital. Burki et al. investigated 11 hypercapnic patients with COPD on invasive ventilation who had failed attempts to wean and subsequently received ECCO₂R therapy [6]. Three patients were weaned, and one patient died due to a retroperitoneal bleed following catheterization. Overall,

Table 1 Notable prospective studies reporting on ECCO₂R for hypoxemic respiratory failure (see Online Appendix for search string)

Name of the first author	Year of publication	Type of study	No. of subjects	Device	Blood flow (mL/min)	Membrane surface (m ²)	Tidal volume on ECCO ₂ R (mL/Kg)	Objectives/outcome measurement	Duration of ECCO ₂ R	Main results
Terragni [30]	2009	Physiological study	32	W. Decap [®] , Hemodac	191–422	0.33	4.2 ± 0.3	Pulmonary cytokines and inflammatory biomarkers	72 h	Reduction of pulmonary cytokines and inflammatory biomarkers
Bein [13]	2013	Randomized Controlled Trial (XTRAVENT study)	79	iLA AV shunt, Novalung	1300 ± 200	1.3	3	VFD at D-28	7.4 ± 4 days	VFD 10 vs 9; NS Postanalysis reported shorter duration of ventilation in more severe hypoxemic patients (P/F ≤ 150)
Fanello [10]	2016	Feasibility and safety study	15	Hemolung/ Alung	435 ± 60	0.59	4	Correct pH and PaCO ₂	24 h	pH and PaCO ₂ corrected. No Side Advert Events related ECCO ₂ R
Schmidt [16]	2018	Multicenter feasibility and safety study	20	W. Prisma lung/ Baxter	421 ± 40	0.32	3.98 ± 0.18	Safety and feasibility of a low-flow ECCO ₂ R	24 h	Safety and feasibility confirmed
Combes [4]	2019	Prospective multicenter international phase 2 study (SUPERNOVA Pilot study)	95	Low flow: Hemolung/ Alung High flow: iLAActive, Xenios; CardioHelp/ Getinge	Low flow: 440 [430;480] High flow: 960 [800; 1000]	0.59 1.30/1.30	4	Proportion of patients achieving ultra-protective ventilation	5 [3–8] days	78% of patients achieved ultra-protective ventilation
McNamee [5]	2021	Randomized Controlled Trial (REST Study)	405	Hemolung/ Alung	350–450	0.59	4.5 [4.3–4.8]	90 day mortality	4 ± 2 days	Trial stopped early because of futility Mortality 41.5% in ECCO ₂ R group vs 39.5% in the standard care group

Table 2 Notable studies reporting on ECCO₂R for hypercapnic respiratory failure (see Online Appendix for search string)

Name of the first author	Year of publication	Type of study	No. of subjects	Device	Blood flow (mL/min)	Membrane surface (m ²)	Tidal volume on ECCO ₂ R (mL/kg)	Objectives/outcome measurement	Duration of ECCO ₂ R	Main results
Kluge [34]	2012	Case-control study	21	iLA AV shunt, Novalung	1300 ± 200	1.3	NIV	To assess efficacy and safety of NIV-plus-ECCO ₂ R to prevent intubation	9 days	90% did not require intubation, similar D28 mortality 24% vs. 19%
Burki [6]	2013	Multicentric pilot study	20	Hemolung/Alung: 0.59	430.5 ± 73.7	0.59	Not reported	Safety and feasibility of a low-flow ECCO ₂ R	104.2 ± 59.7 h range 2–192 h	Safety and feasibility confirmed
Del Sorbo [7]	2015	Paired cohort study with historical control	25	PLP 1.35	255		NIV	To assess efficacy and safety of NIV-plus-ECCO ₂ R to prevent intubation	1–2 h	Intubation-NIV + ECCO ₂ R = 12% vs NIV-only = 33% (p = 0.1495)
Braune [14]	2016	Case-control study (ECLAIR study)	25	ILAActive, Xenios: 1.30	1300	1.3	NIV	To assess efficacy and safety of NIV-plus-ECCO ₂ R to prevent intubation	8.5 h	Intubation was avoided in 14 of 25 patients under ECCO ₂ R (56%). 90-day mortality = 28 vs. 28%

ECCO₂R, extracorporeal carbon dioxide removal; NIV, non-invasive ventilation; VFD, ventilatory free days

Table 3 Non indications and contraindications for ECCO₂R

Non indications	Absolute contraindications	Relative contraindications
Refractory hypoxia (PaO ₂ /FiO ₂ ≤ 80 after recruitment and pron-ing) or other indication for ECMO	Contraindication to anticoagulation	Acute multiple organ failure defined as more than two organ failures assessed by SOFA score
Untreated pulmonary embolism as the primary cause of acute respiratory failure	Severe coagulopathy	Recent major surgery in the last 2 weeks
Pneumothorax or bronchopleural fistula as the primary cause of acute respiratory failure	Anatomical abnormalities or vascular diseases preventing the correct insertion of the ECCO ₂ R cannula	Recent or current use of medications known to increase risk of bleeding
Cardiogenic pulmonary edema as the primary reason for respiratory failure	Severe liver insufficiency (Child–Pugh scores > 7) or fulminant hepatic failure	Acute myocardial infarction or acute coronary syndrome within 30 days
Neuromuscular disease that impairs ability to ventilate without assistance	Heparin-induced thrombocytopenia, known hypersensitivity to heparin or to compounds	Any legally authorized document(s) that may restrict aggressive medical management such as “Do Not Resuscitate,” “Do Not Intubate”
	Ineligibility for lung transplantation according to standard criteria for bridge to transplantation patients	Permanent home ventilation except for sleep-disordered breathing
	Moribund state with established multiorgan failure	Advanced malignancy with life expectancy ≤ 6 months
		Immunocompromised state
		Body mass index > 40
		Patients in chronic dialysis
		Sepsis and bacteremia

ECCO₂R, extracorporeal carbon dioxide removal; ECMO, extracorporeal membrane oxygenation; SOFA, Sequential Organ Failure Assessment

these results show that ECCO₂R may be a promising therapy in patients with acute hypercapnic respiratory failure, both for avoiding intubation and for weaning. However, randomized trials are still pending to further elucidate the relative benefit and risks [4].

Other indications

In severe acute asthma patients, when dynamic hyperinflation or life-threatening respiratory acidosis persists despite optimal medical and ventilator management, ECCO₂R could be beneficial by minimizing dynamic hyperinflation and intrinsic PEEP [3]. In a recent retrospective study of 26 consecutive mechanically ventilated patients with status asthmaticus and refractory hypercapnia [36], 76% were extubated while receiving ECCO₂R and all patients (100%) survived to hospital discharge.

ECCO₂R may be also indicated in patients awaiting lung transplantation because of end-stage hypercapnic lung disease or pulmonary fibrosis [8, 37]. It allows for the correction of respiratory acidosis and enables spontaneous breathing, keeping these patients awake and ambulatory during bridging. Data supporting its use in these patients, as well as in end-stage cystic fibrosis patients, are very encouraging with 1-year survival reaching 80%

but limited to cases and small patient cohorts or subsets of larger cohorts [38]. Anecdotally, ECCO₂R (AV) was used in 5 patients suffering from brain injury and concomitant respiratory failure, with a goal of decreasing PaCO₂ and the accompanying elevated intracranial pressure [39]; 4 of these patients had favorable outcomes.

Contraindications and non-indications (Table 3)

For all potential indications, patients would generally not be considered suitable for an ECCO₂R strategy if they meet the indications for ECMO, if anticoagulation is contraindicated or if they have major comorbidities and/or predicted survival < 1 year, (Table 3), [3, 8]. Of note, in patients suffering from end-stage pulmonary fibrosis, ineligibility for lung transplantation is an absolute contraindication [2, 40].

Patient management

Anticoagulation under ECCO₂R

Unfractionated heparin is the first line anticoagulant during ECCO₂R [3], with an initial intravenous bolus (40–80 IU/kg PBW), except for patients already on full anticoagulation. Experts recommend monitoring of anticoagulation with activated partial thromboplastin time

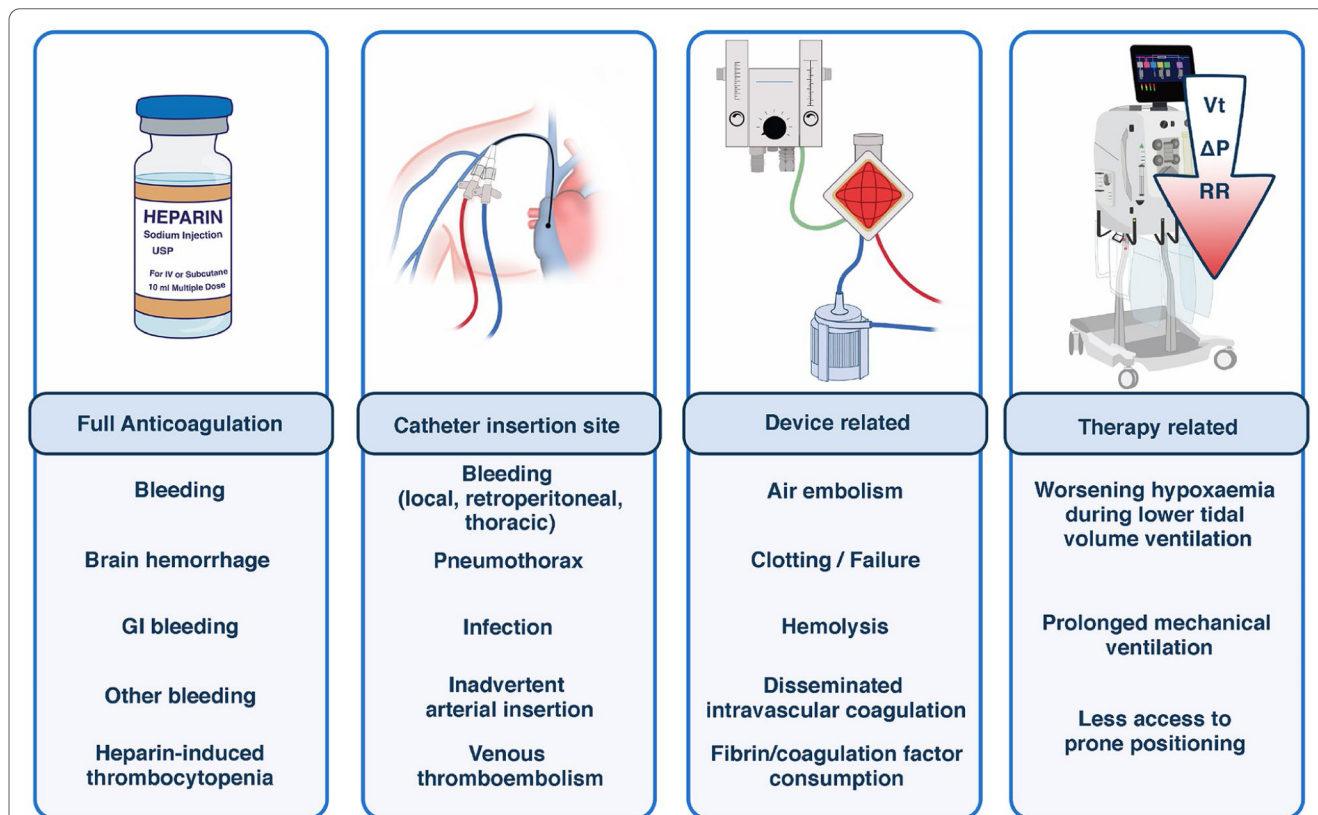


Fig. 2 Adverse events in patients receiving ECCO₂R

(aPTT) and/or anti-Xa activity, with therapeutic goals of 1.5–2.0 times control and 0.3–0.5 IU/mL, respectively [3]. Of note, although cases of proven heparin-induced thrombocytopenia are rare in patients under ECLS [41, 42], intravenous argatroban is the first line anticoagulant recommended in this situation [3, 43].

Other objectives

The overall management of respiratory failure patients under ECCO₂R should not be different than in non-ECCO₂R patients and follow recent guidelines [44, 45]. Specifically, in patients with ARDS, prone positioning should be continued when indicated [44, 45]. Targeting a higher PEEP to maintain a constant mean airway pressure has been proposed to reduce atelectasis, shunt and hypoxemia related that may result from lowering the intensity of mechanical ventilation [4].

Complications associated with VV-ECCO₂R

Although ECCO₂R is often regarded as being less invasive than ECMO and therefore should be associated with lower complication rates (Fig. 2), accumulating evidence suggests that this may not be correct [31, 46–49]. Specifically, rates of hemolysis and hemorrhagic and thrombotic complications are frequently higher in ECCO₂R than in ECMO patients. There are several potential mechanisms for the increased complications with ECCO₂R in large part because the systems were optimized to be used as ECMO at relatively high blood flow rates (>~4 L/min). For example, when the centrifugal blood pumps used in most ECCO₂R systems are used at low flows (<1 L/min) there may be decreased hydraulic efficiency of the pump, leading to increased blood stagnation and recirculation, which may result in increased hemolysis [50]. Lower blood flows may also lead to inhomogeneous blood flow distribution, insufficient washout and blood stagnation through large membrane lungs resulting in early thrombosis [50], which frequently motivates the use of higher anticoagulation. Indeed, beyond the occurrence of ECLS-associated coagulopathy (acquired von Willebrand syndrome [51], thrombocytopenia and consumption of coagulation factors [28]), the higher anticoagulation (compared to ECMO) recommended to prevent early clotting of current ECCO₂R devices exposes patients to a significant risk of severe hemorrhagic complications [5, 10, 28, 47]. The incidence of bleeding events may be associated with the duration of ECCO₂R, with most events commonly occurring after 5 days of ECCO₂R in the ECLAIR study [14].

In the REST trial there were serious adverse events in 62 patients (31%) in the ECCO₂R group vs 18 (9%) in the control arm. Bleeding (excluding intracranial hemorrhage) and intracranial hemorrhage occurred in 17 (8.4%)

vs. 3 (1.4%) of the ECCO₂R patients, and 9 (4.5%) vs. 0% of the control patients, respectively. In addition, three intracranial bleeding episodes occurred in the ECCO₂R group but were not classified as serious adverse events (SAEs) by site investigators [5]. In the SUPERNOVA study [48], bleeding events were reported in 14% of patients, with intracranial hemorrhage occurring in only one of 95 treated patients. A higher rate of bleeding (21% vs. 6%) was reported in the 33 ARDS patients treated with a lower CO₂ extraction device, compared to the 62 ARDS patients treated with two higher CO₂ extraction ECCO₂R devices [48]. However, the association of complication rates with specific device is difficult to determine as there are no randomized comparative trial data between devices.

Due to the typically lower blood flow rates and the smaller membrane surface areas used in veno-venous ECCO₂R (VV-ECCO₂R) compared to veno-venous ECMO (VV-ECMO), there is a greater risk of catheter and/or membrane thrombosis [50]. Membrane clotting could reduce membrane CO₂ clearance, increase trans-membrane pressure, and cause more frequent membrane changes and premature withdrawal of the device, with the interruption of ultra-protective ventilation permitted by ECCO₂R. Depending on the technology used, the incidence of this adverse event could vary widely. For instance, a significantly lower incidence of membrane clotting was reported with devices with higher CO₂ removal and greater blood flow rates (800–1000 mL/min) (14%) compared to low CO₂ removal devices, despite a similar anticoagulation regimen in the SUPERNOVA study [4, 48]. In addition, Schmidt et al. reported a 50% incidence of clotting with the PrismaLung device (Baxter®), which provided CO₂ removal through a classical dialysis catheter and with lower blood flow rates (i.e., 425 mL/min) [16]. This phenomenon, occurring despite a high anticoagulation regimen with aPTT ratio at 1.8 and 230 IU/kg/h of continuous unfractionated heparin (UFH) infusion, led to early withdrawal of ECCO₂R in 50% of the patients after only 20 h of therapy [16]. To decrease the incidence of bleeding and thrombotic events in ECLS patients, better methods for monitoring anticoagulation may be warranted and of utmost importance new devices requiring less or only regional anticoagulation. However, a lack of association between laboratory monitoring tests commonly used for managing anticoagulation, and observed bleeding and clotting in ECLS patients is frequently reported and no best practice methods have been identified [52, 53]. Beside classic coagulation parameters, markers of endothelial damage and dysfunction deserve further exploration to predict both bleeding and thrombosis along with anticoagulation level adjustment [54–57].

Furthermore, it should be noted that although some retrospective data suggested that lower ΔP and PowerRS during mechanical ventilation for ARDS were associated with lower mortality, we still lack strong scientific evidence demonstrating that applying ultraprotective ventilation targeting a decrease in these parameters would improve patients' outcomes. Indeed, there are a number of mechanisms by which ultraprotective ventilation might paradoxically worsen outcomes. First, decreasing the intensity of mechanical ventilation may be associated with lower airway pressure, lung de-recruitment, atelectasis and atelectrauma, leading to worsening hypoxemia. Hypoxemia may also be worsened because the respiratory quotient decreases when ECCO₂R is applied, leading to lower alveolar PaO₂ for the same FiO₂ [58]. In the REST trial, the median PaO₂/FiO₂ decreased in the ECCO₂R group while it increased in the control group in the first 3 days of treatment and the recourse to ECMO in ECCO₂R patients was increased although the difference between groups did not reach statistical significance. Second, prone positioning may be used less frequently in ECCO₂R patients (e.g., 5% vs. 14% on day 1 in the REST trial). To the extent that the prone position decreases VILI, lower use of this approach may lead to worse outcomes. Lastly, targeting lower respiratory rate may also require deeper sedation and sometimes muscle paralysis, that may be associated with prolonged mechanical ventilation, as reported in the REST trial [5].

Other ECCO₂R related complications include hemolysis, reported in 12% of patients in the SUPERNOVA pilot study [4], and 1.5% of patients in the interventional group of the REST trial [5]. The daily measurement of serum-free hemoglobin and lactate dehydrogenase may allow earlier detection of hemolysis and avoid progression to acute kidney injury [59]. Local infectious complications have been reported, albeit rarely. For instance, they occurred in only two patients in the SUPERNOVA pilot study [32]. Lastly, severe arterial complications such as limb ischemia, compartment syndrome or femoral artery pseudoaneurysm have dramatically decreased following the virtual discontinuation of pumpless arterio-venous ECCO₂R [31]. However, there are reports of severe complications related to vascular access, such as perforation of the iliac vein, retroperitoneal bleeding or pneumothorax at cannula insertion [4, 6, 7].

Resources, costs, infrastructure and quality assurance for ECCO₂R

With no conclusive clinical evidence and relatively high rate of associated complications, this technique should only be implemented in the context of trials or registries [3, 8] and in centers experienced in the care of patients

with the underlying diseases that motivate the use of ECCO₂R [8, 60]. While the management of low-flow, roller pump driven ECCO₂R devices (low flow systems) should resemble continuous renal replacement therapy, ECCO₂R devices based on ECMO platforms may require additional experience, and special training programs [61–64], as would dedicated ECCO₂R devices. Continuing education including simulation training of every staff member will be essential to ensure the quality, efficiency and sustainability of an ECCO₂R program [60–64].

Quality indicators will need to follow the three domains of healthcare: structure, process and outcomes [65], with repeated audits and reviews of clinical outcomes and associated adverse event [8, 66]. Data from studies on CRRT have shown that up to 30% of patients do not receive the minimum standard of care and specific programs to address the quality of CRRT care frequently do not exist [66, 67].

Costs and cost-effectiveness of the technique should also carefully be evaluated. In the ECMO field, large cost difference in studies have been reported between US and non-US studies [68, 69]. In COPD patients, using data from a retrospective analysis of patients on the no-longer used arterio-venous (AV) ECCO₂R [34], German authors found that the treatment was cost-effective with significantly lower median intensive care unit (ICU) length of stay (11.0 vs. 35.0 days), hospital length of stay (17.5 vs. 51.5 days) and costs for the ECCO₂R group [70]. A theoretical model based on data from the LUNG SAFE study [71] and the putative survival benefits associated with lowering driving pressure based on an analysis of more than 3000 patients enrolled in 9 randomized ARDS trials [22], demonstrated incremental cost-effectiveness ratios (ICERs) below the €50,000 threshold with ultra-protective lung ventilation enabled by ECCO₂R in patients with ARDS [72]. However, recent results from the REST trial clearly questions the validity of this cost benefit ratio of ECCO₂R [5], highlighting the need for well-designed clinical and cost-effectiveness studies.

Current and future research priorities

ECCO₂R has the potential to shift our approach for treating both acute hypercapnic and acute hypoxemic respiratory failure. However, for ECCO₂R to gain traction in clinical practice, rigorous clinical trials—informed by mechanistic studies—with meaningful, patient-centered outcomes are needed. The field would be well-served to organize research collaboratively around networks and medical societies capable of promoting high-quality research [8, 60, 61, 73, 74], and to define a research agenda as well as core datasets and core outcome sets to inform the design of future studies [73–76].

The current focus is centered on the use of ECCO₂R for ARDS and for acute exacerbations of COPD. However, there are other potential indications, such as severe acute exacerbations of asthma [36] and bridge to lung transplantation [37, 38], although conducting trials to get high scientific evidence may be highly challenging in these settings. Regarding ARDS, the results of the REST trial [5] should give us pause. However, the REST trial answered a specific question under particular trial conditions and with a single device, and thus does not negate the possibility of benefit of ECCO₂R in some other form for patients with ARDS. Interestingly, a follow-up study [32] of the SUPERNOVA pilot trial [4] evaluated the variability and determinants of the effect of ECCO₂R on V_T , ΔP , PowerRS with the aim to determine whether highly responsive patients can be identified for the purpose of predictive enrichment in ECCO₂R trial design. Greatest reduction in V_T , ΔP , and PowerRS with ECCO₂R was observed in patients with higher baseline alveolar dead space fraction or lower respiratory system compliance and when higher CO₂ extraction devices were used. Restricting enrolment to patients with a larger predicted decrease in ΔP might indeed enhance the average reduction in ΔP , increase predicted mortality benefit, and reduce sample size and screening size requirements for future trials of ECCO₂R.

As for COPD, there are several ongoing or planned randomized clinical trials (RCTs) examining the use of ECCO₂R for acute exacerbations of COPD in lieu of or in addition to invasive mechanical ventilation. While early studies have shown promise [7, 14, 35], RCTs are surely needed to adjudicate the balance of the potential benefits and the known risks.

In a technology-dependent field, the risk-to-benefit ratio of ECCO₂R in the clinical setting will always be dependent on both the capabilities and the adverse effects associated with the device used in a given study or clinical scenario. As the technology of ECCO₂R is evolving quickly, the nature of providing ECCO₂R and the risk-to-benefit ratio is a moving target that will make definitive answers about the efficacy of ECCO₂R for any given indication difficult to provide, as those answers may be supplanted over time by trials performed with newer technology. In addition, advances in technology may enable the transition of ECCO₂R from an ICU-based strategy competing against mechanical ventilation, to a fully artificial lung whose applications could be transformative [8, 77].

Finally, it will be key to look beyond mortality as an outcome, and RCTs as a methodology. We will need physiologic data, quality of life and long-term outcome data, which may be delivered in the form of propensity

matching, adaptive trial designs, registry randomized trials and other approaches that may best inform the clinical questions at hand.

Conclusion

ECCO₂R has been increasingly used in patients with respiratory failure, despite the lack of high-quality evidence, and the negative results of a recent randomized trial in patients with acute hypoxemic respiratory failure [5]. The indications and the risk-to-benefit ratio of this technique should now be carefully evaluated using structured national or international registries and future large randomized clinical trials. Organizations such as the International ECMO Network (ECMONet) [78] can provide guidance on the design and coordination of such studies.

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Declarations

Conflicts of interest

AC reports grants and personal fees from MAQUET, Xenios, and Baxter. AC was a past president of EuroELSO and is a member of the executive and scientific committees of ECMONet. DB reports research support from ALung Technologies, and personal fees from Abiomed, Xenios, Medtronic, Inspira and Cellenkos. DB is the President-elect of the Extracorporeal Life Support Organization (ELSO) and the Chair of the Executive Committee of the International ECMO Network (ECMONet). GC reports personal fees, travel expenses from Baxter and Fresenius. JLD reports research supports, grants and personal fees from

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