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REVIEW

Hypercapnia and extracorporeal carbon dioxide removal ($ECCO_2R$) in the acute respiratory distress syndrome

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Abstract

As a result of technical improvements, extracorporeal techniques for carbon dioxide removal have become an attractive option in managing adults with acute respiratory failure. However, evidence to support its use is scarce, and several questions regarding the best way to implement this therapy remain unanswered, which can be associated with severe side effects. In this review, we will present the currently available knowledge on (1) $ECCO_2R$ as an adjuvant treatment to invasive mechanical ventilation, (2) the impact of hypercapnia in patients with acute respiratory distress syndrome (ARDS), (3) the pathophysiological rationale and evidence of $ECCO_2R$ in patients with ARDS.

Keywords

Acute respiratory distress syndrome; Extracorporeal carbon dioxide removal; Carbon dioxide; Lung-protective ventilation; Ventilator-associated lung injury

1. Background

Acute hypoxemic respiratory failure, and its most severe form, acute respiratory distress syndrome (ARDS), is a leading cause of admission to the intensive care unit (ICU). It is associated with significant mortality and long-term morbidity for survivors and considerable resource utilization for health care systems [1].

In critically ill patients with acute hypoxemic respiratory failure, mechanical ventilation is a life-saving treatment [2]. At the same time, this therapy can cause ventilator-induced lung injury (VILI), a lung injury condition inflicted or aggravated by mechanical ventilation during treatment. Multiple evidence demonstrated that excessive lung stress and strain, induced by excessive transpulmonary pressure, results in regional alveolar overdistension or cyclic opening and closing of distal airways, which cause lung injury [3]. In recent years, much effort has been invested in understanding the pathophysiology of VILI, which has led to notable changes in ventilation management and remarkable improvement in patient outcomes. For instance, while it was common practice to use "unphysiological large" tidal volumes to prevent atelectasis and target normal gas exchange, it is now widely accepted to use low pressures and low tidal volumes to protect the lungs against VILI [2, 4]. In a seminal study, the ARDSNet investigators showed significantly higher mortality with a high tidal volume (V_T) strategy of 12 mL/kg of predicted body weight (PBW), as compared to a low $V_T$strategy of 6 mL/kg PBW and limiting end-inspiratory plateau pressure (P_{PLAT}) to $\leq$ 30 cmH_2O [5]. However, the reduction in tidal volume and inspiratory pressures results in the development of respiratory acidosis, which is tolerated within certain safe limits, according to the notion of "permissive hypercapnia".

Nonetheless, in some patients, even lung-protective ventilation (LPV) settings may not be fully protective [6, 7]. Up to one-third of patients receiving lung-protective ventilation had evidence of tidal hyperinflation and, hence, risk of VILI [6]. Moreover, data from large observational studies suggest that there might not be a safe threshold for tidal volume or driving pressure due to the heterogeneity of lung injury [8, 9]. These data prompted the hypothesis that further reducing tidal volume and driving pressure could result in less VILI and patient-centered outcome improvement [10].

This strategy would potentially entail an unacceptably high risk of life-threatening respiratory acidosis [11] due to significantly reducing alveolar ventilation with tidal volumes equal to or inferior to physiologic dead space. To overcome this issue and facilitate "ultra" protective strategies of mechanical ventilation to minimize VILI, increasing interest has been focused on extracorporeal carbon dioxide removal ($ECCO_2R$) since the first reports in the 1980s [12–14].

2. Pathophysiologic rationale of $ECCO_2R$ in ARDS

One of the major clinical challenges in ARDS and hypoxemia is carbon dioxide (CO_2) clearance and the strategy to best achieve it. However, the optimal physiologic and metabolic

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targets to provide adequate homeostasis without inducing VILI are not yet defined, as highlighted above, suggesting a potential role for $ECCO_2R$.

In patients with ARDS, hypercapnia develops due to decreased alveolar ventilation, determined by the variable combination of alveolar collapse/infiltrate and increased alveolar dead space. Alveolar infiltrates, and collapse is unevenly distributed throughout the lung, with smaller preserved aerated zones, defined as "baby lung" [15]. Physiological dead space (V_D/V_T) is the sum of the anatomical and alveolar dead spaces and is defined as all parts of the tidal volume that do not participate in gas exchange. V_D/V_T comes from respiratory units that receive disproportionately low perfusion compared with ventilation ($Q < V$), resulting in an increasing "West Zone 1" physiology [16]. High alveolar dead space (VD_{ALV}) may result from endothelial injury, microvascular thrombi, and overdistention of alveoli during mechanical ventilation [17, 18]. V_D/V_T during the first seven days after ARDS diagnosis is an independent lung-specific physiological variable associated with increased mortality [19, 20]. However, dead space measurements are not routinely performed in clinical practice to guide patient management due to the challenges of the various measurement strategies [21]. Other methods for estimating V_D/V_T, which do not require quantitative assessment of exhaled carbon dioxide, are easier to use at the bedside. Recently, the ventilatory ratio and end-tidal-to-arterial Partial pressure of carbon dioxide (PCO_2) ratio have been described as surrogates for V_D/V_T in ARDS patients [22–25].

2.1 Hypercapnia in ARDS

The effects of hypercapnia have been extensively studied in clinical and experimental investigations, but the results are conflicting. Thus, the definition of adequate CO_2 and pH clinical targets remains challenging.

Hickling *et al*. [26] were the first to propose protective ventilation strategies as the rescue therapy for patients with severe ARDS to limit VILI. These strategies include the following measures: (1) low peak inspiratory pressure and low V_T ventilation; (2) use of positive end-expiratory pressure (PEEP); and (3) acceptance of higher partial pressure of arterial carbon dioxide ($PaCO_2$) levels. Despite its limitations, this study showed significantly lowered hospital mortality by adapting the protective ventilation strategies. This finding led to a series of clinical investigations in patients with ARDS, including the potential protective role of permissive hypercapnia [5, 8, 27–29]. Regretfully, important limitations of these studies, such non-randomization of patients to receive normocapnia or hypercapnia, have precluded the conclusive demonstration of a direct protective effect of high CO_2 in these patients.

To advance the knowledge on this issue, several experimental studies have also investigated the potential protective effect of hypercapnia on mechanisms of acute lung injury [30]. In an experimental model of rabbit lungs ventilated *ex-vivo* with high pressures, hypercapnia decreased microvascular permeability, lung edema formation, and protein concentration in the bronchoalveolar lavage fluid [31]. The plausible mechanisms are (1) the CO_2 action, through nuclear factor-kappa ($NF\kappa B$) pathway activation, preventing p65 translocation and thereby reducing inflammation [32, 33]; (2) CO_2 inhibition of the ADAM-17 (a disintegrin and metalloprotease domain enzyme), which prevents the activation of the p44/p42 MAPK (mitogen-activated protein kinases pathway) [34].

Hypercapnia has also been shown to reduce apoptosis in rat lungs exposed to high-pressure ventilation by inhibiting the activation of the MAPkinase and stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) pathways in alveolar epithelial cells [35].

In contrast to its beneficial effects, the potentially detrimental effects of hypercapnia on mechanisms of injury have also been studied. It has been observed that high levels of CO_2 impaired the phagocytic activity of neutrophils in rat models [36]. Furthermore, hypercapnia decreased alveolar cell proliferation and delayed wound repair in different types of human lung cells in pH-independent and dose-dependent ways [37]. Hypercapnic acidosis impairs membrane wound resealing [38, 39] in *ex-vivo* and *in-vitro* rat models of VILI. High CO_2 levels have been found to decrease the clearance of alveolar edema through inhibition of the Na^+-K^+-ATPase pump through an endocytosis process [40] that is pH independent [41]. Lastly, hypercapnia may modulate innate immunity and host defense via pH-independent or dependent mechanisms [42, 43]. High CO_2 levels suppress innate immunity by inhibiting mRNA and the expressions of inflammatory cytokines (IL-6 and TNF-α) and autophagy in alveolar macrophages in rats [43, 44]. The biological actions of CO_2 are depicted in Fig. 1.

Although progressively adopted or tolerated in patients with ARDS to facilitate protective mechanical ventilation settings, permissive hypercapnia has considerable pathophysiological effects, which need to be considered. Hypercapnic acidosis can increase pulmonary vascular resistance and worsen pulmonary hypertension, potentially increasing right ventricular afterload and triggering acute cor pulmonale. It also impairs diaphragmatic function through afferent transmission or integrity with short-term exposure to moderate hypercapnia in preclinical models [45, 46]. Hypercapnia causes precapillary cerebral arteriole dilation, increasing cerebral blood flow, a clear concern in the setting of reduced intracranial compliance, in which increased global cerebral blood flow may critically elevate intracranial pressure. Moreover, hypercapnic acidosis directly reduces the contractility of cardiac and vascular smooth muscle [47, 48]. However, this is counterbalanced by the hypercapnia-mediated sympathoadrenal effects, including increased preload and heart rate, increased myocardial contractility, and decreased afterload, leading to a net increase in cardiac output [48, 49].

A recent secondary analysis of three international studies on patients with ARDS showed that severe hypercapnia, defined as $PaCO_2$ 50 mmHg, was independently associated with higher ICU mortality and multiorgan failure [50]. Interestingly, the number of patients with severe hypercapnia progressively increased from 1998 to 2010, mirroring the progressively higher adoption of lung protective ventilation, which may reflect the belief of the beneficial effect of hypercapnia.

In another retrospective analysis of mechanically ventilated patients, it was observed that patients who developed respiratory acidosis (pH <7.35 and $PaCO_2$ >65 mmHg) during the first 24 hours of ventilation had a worse prognosis compared

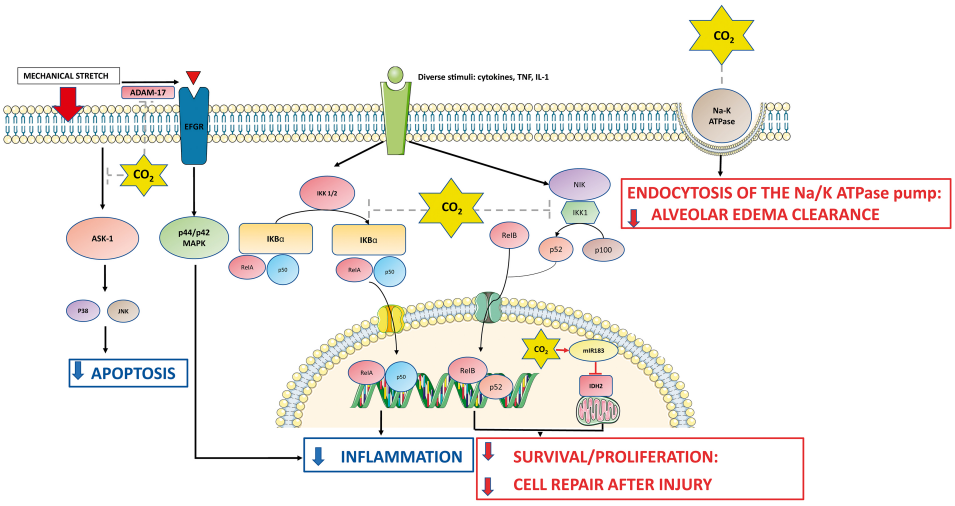

FIGURE 1. Schematic depiction of CO_2 actions at cellular level with its positive (BLUE) and negative effects (RED). Left: Mechanical stretch induced phosphorylation of p44/p42 is decreased by CO_2 inhibition of ADAM-17. Apoptosis is decreased by hypercapnia by impairment of ASK1-JNK/p38 MAPK pathway. Right: CO_2 acts upon the NF-κB pathway after inflammatory stimuli. Carbon dioxide inhibits IκB-α degradation, impairing ReIA/p50 translocation into the nucleus exerting its anti-inflammatory effects. On the other hand, CO_2 impairs alveolar cell proliferation by inhibiting IKK/NIK complex impairing ReIB/p52 formation via the NF-κB complex and also by inducing miR183 which down-regulates IDH2 producing mitochondrial dysfunction (independent of NF-κB pathway). Hypercapnia- induced endocytosis of the Na,K-ATPase transporter. ADAM-17: disintegrin and metalloproteinase 17; MAPK: mitogen-activated protein kinases; ASK: Apoptosis signal-regulating kinase 1; JNK: c-Jun N-terminal kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1: interleukin1; TNF: Tumoral necrosis factor; IDH2: isocitrate dehydrogenase-2; NIK: NF-κB-inducing kinase; IKK: IκB kinase; EFGR: epidermal growth factor receptor; CO_2: carbon dioxide.

to those who had normocapnia or compensated hypercapnia [51].

The "Large observational study to UNderstand the Global impact of Severe Acute respiratory FailurE" (LUNG SAFE) study, a worldwide multicenter observational investigation in ventilation practice in patients with ARDS [52], reported the prevalence and impact of changes in CO_2 on ventilation management and outcomes in patients with early ARDS. This observational study showed that hypocapnia and hypercapnia are commonly present, and in approximately half of the patients, CO_2 derangements are sustained over the first two days of ventilation. Interestingly, there was no mortality difference between normocapnic and hypercapnic patients, concluding that there is no evidence for hypercapnia to be considered beneficial or harmful. Of note, the LUNG SAFE investigators also show ICU mortality to be higher in hypocapnic compared to normocapnic patients with mild-to-moderate ARDS, suggesting the need for caution with sustained hypocapnia.

The above-discussed evidence suggests that the application of $ECCO_2R$ could be beneficial to improving metabolic homeostasis and minimizing VILI, which is achieved by allowing the delivery of ultra-protective mechanical ventilation settings and avoiding the potentially detrimental hemodynamic and neurological consequences of hypercapnia. It is increasingly recognized that CO_2 is more than just a product of cellular metabolism and that hypercapnia can regulate several critical biological functions in the lung, which could be detrimentally altered by inadequate $ECCO_2R$ application.

3. Principles and technical aspects of $ECCO_2R$

3.1 Principles

The $ECCO_2R$ devices consist of a drainage cannula placed in a large central vein or artery (the latter if an arterio-venous configuration is used, which is not often), a pump, and a gas exchanger (artificial membrane lung), and a return cannula into the venous system. Gas exchange is achieved through an extracorporeal artificial lung unit containing a diffusion membrane. In this unit, blood is passed through hollow plastic fibers with a mesh-like pattern that increase the surface area for membrane-to-blood contact and gas exchange efficiency. Via the surface of the membrane fibers, the exchange of oxygen and CO_2 occurs by diffusion. The efficiency of each device (*i.e.*, the volume of CO_2 removed per minute, adjusted to blood flow) should be an important consideration for clinicians since it determines the blood flow rate and hence the catheter size needed for adequate CO_2 removal. To obtain an efficient membrane lung with the lowest necessary amount of membrane surface, a design incorporating short fibers that allows a maximal sweep gas ratio is required to keep the gradient over the entire length of the fiber at its highest possible level. This is in contrast to extracorporeal membrane oxygenation (ECMO), which requires high flow rates to increase arterial blood oxygenation. $ECCO_2R$ needs considerably lower blood flow rates as the gas dissociation curves in blood for oxygen and CO_2 are significantly different.

Theoretically, due to the higher diffusion coefficient of CO_2,

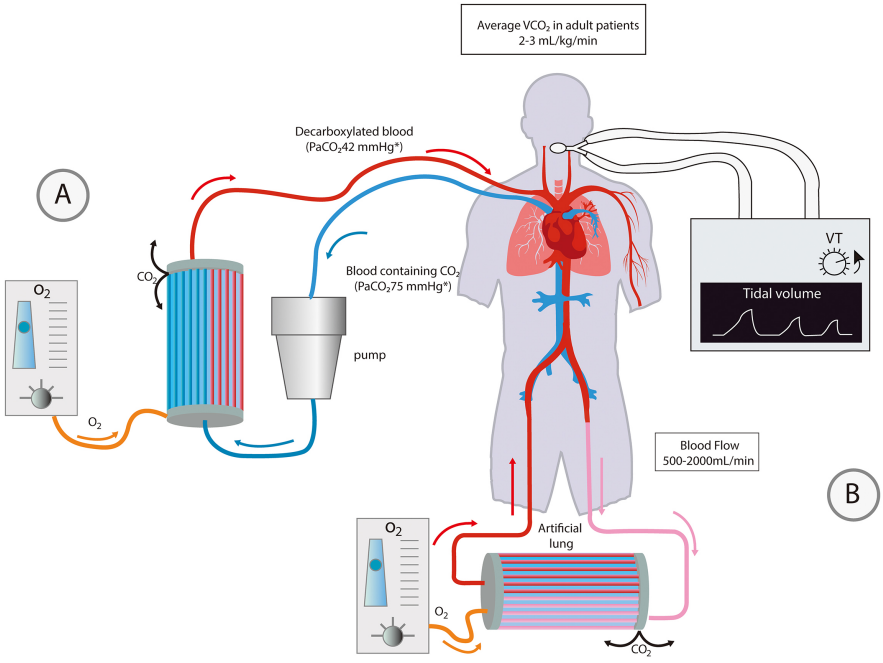

FIGURE 2. Use of $ECCO_2R$ to decrease the injury induced by mechanical ventilation. Figure depicts the common configurations used. A. Veno-venous $ECCO_2R$ configuration with a double-lumen catheter inserted into a central vein. B. Arterio-venous $ECCO_2R$ configuration with the positioning of the exchange membrane linking the femoral artery and vein. No pump is needed. $PaCO_2$: partial pressure of carbon dioxide in arterial blood; VCO_2: carbon dioxide production; CO_2: carbon dioxide; O_2: oxygen; V_T: tidal volume.

blood flow of ~1 L/min is sufficient to remove the entire CO_2 production of an average-sized patient effectively. In contrast, relevant oxygenation of the blood only occurs with blood flows of approximately 50–60% of the cardiac output. Therefore, an $ECCO_2R$ system requires smaller cannulas and lower blood flow. In $ECCO_2R$, the sweep gas flow is kept high to maximize the effectiveness of CO_2 elimination through the artificial membrane from the blood.

Before initiating the extracorporeal CO_2 elimination, it is necessary to estimate the patient's CO_2 production (on average, about 250 mL/min in the critically ill patient under resting conditions [53]) and, on the other hand, the therapeutic goal. With low flow rates in the 200–450 mL/min range, it is possible to eliminate an average of CO_2/min corresponding to about 20–30% of the average CO_2 production [54, 55] as demonstrated in recent clinical trials [56, 57].

Recent preclinical research has investigated ways to increase the efficiency in CO_2 removal by techniques that acidifies blood in the extracorporeal circuit and by using electrodialysis with encouraging results [58–60].

3.2 Technique

Due to the much higher diffusion capacity of CO_2 than O_2, different configurations of extracorporeal CO_2 elimination are possible. The system's configuration depends on the election of the vascular access (arterial or venous) and the type of cannulas that will be used. A distinction is made between pump-driven *vs.* arterio-venous pumpless systems (Fig. 2).

3.2.1 Arterio-venous $ECCO_2R$ (AV-$ECCO_2R$)

$ECCO_2R$ with arterio-venous configuration utilizes the patient's arterio-venous pressure gradient to pump blood through the artificial lung. Vascular access is most commonly obtained by cannulating the femoral artery and vein using the percutaneous technique. Mean arterial pressure greater than 60 mmHg and a cardiac index >3 L/min/m^2 provide flow rates ranging between 0.5 and 1.2 L/min. This configuration is unsuitable for hemodynamically unstable or heart failure patients [61, 62].

The major advantage of the system is the absence of blood trauma due to a pumpless system and thus pump-associated complications. However, this benefit is outbalanced by the risk of distal ischemia, which can occur on the side of the arterial cannulation. The pumpless arterio-venous system introduces a new vascular bed to the patient, which adds an additional burden to the heart that already has to pump blood through the brain, liver, kidneys, and other organs. Given the complications associated with cannulation, its use has fallen out of interest.

3.2.2 Veno-venous $ECCO_2R$ (VV-$ECCO_2R$)

Veno-venous $ECCO_2R$ systems utilize a pump to generate flow across a membrane. To date, pump-driven systems are by far the more used systems. They enable a jugular or femoral double lumen cannula of a size between 20 and 23–24 Fr, allowing blood flows around 500–1000 mL/min. Smaller cannulas can also be considered for lower blood flow, decreasing the cannulation risk. A hemodialysis catheter with 11.5 or 13.5 Fr can generate blood flows of up to 300 mL/min but has a relatively high recirculation rate [63], thus reducing the system's efficiency.

The pumps can be roller (peristaltic) or rotary (centrifugal). The latter has a rotating impeller which creates a suction vortex that draws blood into the center of the pump and propels it outwards from the outlet. The system, which evolved from dialysis, is driven by roller pumps and uses 200 to 450 mL/min of corresponding blood flows. In contrast, the systems developed from ECMO often have flow rates of 0.5 to a maximum of 2.0 L/min using a centrifugal pump [64].

Compared to the AV configuration, one of the gains of VV-$ECCO_2R$ is that it is less invasive as arterial cannulation is avoided and that patients can potentially be mobilized earlier. We recommend VV-$ECCO_2R$ over AV-$ECCO_2R$ in most circumstances unless the centers are already familiar with this technology.

4. Evidence of $ECCO_2R$ in ARDS

$ECCO_2R$ was first proposed in the 1980s when the detrimental effect of VILI was still vastly unrecognized and ignored. The evolving conceptual paradigm of $ECCO_2R$ clinical application was to use extracorporeal support to rest the lung and avoid VILI from high volume and pressure ventilation [14]. Interestingly, in small clinical series, the application of $ECCO_2R$ was reported to decrease barotrauma in patients with ARDS [13, 14] before large clinical trials could demonstrate the benefit of lung-protective ventilation. However, to date, no high-quality evidence has shown the efficacy of $ECCO_2R$ in improving patient outcomes.

A recent meta-analysis of 14 studies with pumpless and pump-driven $ECCO_2R$ [65] has shown that the technique can achieve a sustained reduced partial pressure of arterial CO_2 to 40–50 mmHg and increased blood pH to 7.30–7.45 and a significant increased PaO_2/FiO_2 ratios; these while decreasing V_T~3 mL/kg/IBW (ideal body weight), and P_{PLAT} by at least 5 cmH_2O, maintaining a PEEP level of around 15 cmH_2O. The device duration was between 7 to 14 days. However, there was no effect on mortality or clinically relevant outcome measures.

The SUPERNOVA study investigated the role of ultra-protective ventilation in patients with early moderate ARDS under invasive mechanical ventilation [66]. Ultra-protective ventilation consisted in targeting tidal volumes of 4 mL/kg and $P_{PLAT} \leq$ 25 cmH_2O. The main outcome was the proportion of patients achieving ultra-protective ventilation without developing respiratory acidosis (pH <7.30 while maintaining $PaCO_2$ around 20% of baseline values with Vt 6 mL/kg IBW). Devices with different CO_2 extraction rates were used. $ECCO_2R$ was kept for 3–8 days. $ECCO_2R$ was able to significantly reduce P_{PLAT} from 26 $\pm$ 5 cmH_2O to 23 $\pm$ 3 cmH_2O in 73% of patients, with a reduction of driving pressure from 13 $\pm$ 5 to 9 $\pm$ 4 cmH_2O. Few adverse effects were related to the use of $ECCO_2R$. These findings showed that in this study, $ECCO_2R$ was feasible and safe. A secondary analysis of the data from the SUPERNOVA study demonstrated that the magnitude of reduction in VT, driving pressure, and mechanical power permitted by $ECCO_2R$ is significantly higher in ARDS patients with higher dead space (determined by a ventilator ratio (VR) >2) or lower compliance of the respiratory system (Crs) or treated with a higher CO_2 extraction rate device [67].

Finally, although these data confirmed the technique's feasibility with consistent physiological effects, the lack of patient-centered outcomes warranted further investigation.

Several studies have shown the feasibility and efficiency of $ECCO_2R$ in removing significant amounts of CO_2 to facilitate very low tidal volume mechanical ventilation strategies [66, 68]. However, these studies were not designed to investigate the efficacy of this technique in improving patient-centered outcomes.

Recently a large, randomized, controlled, open, phase 3 pragmatic clinical and cost-effectiveness trial led by experienced clinical trials group [57] tried to respond to the clinical question of whether $ECCO_2R$ improves day 90 all-cause mortality in mechanically ventilated patients with acute hypoxemic respiratory failure. The original plan was for an interim analysis of 560 patients. However, this was moved forwards to 412 patients after the trial was paused to investigate an intracranial hemorrhage in the intervention arm. At this time point, the Data and Safety Monitoring Board (DSMB) performed a conditional power analysis and found that ongoing recruitment was unlikely to show benefit. 202 patients were randomized to the experimental arm and 210 to the control arm. Tidal volumes, inspiratory plateau pressure, and driving pressure were lower in patients randomized to the intervention arm than controls, as per the study design. However, although mean ventilator-free days were significantly lower in the $ECCO_2R$ group (mean difference, –2.1 (95% CI, –3.8 to –0.3); $p = 0.02$), no difference was found in the primary outcome of day 90 all-cause mortality, 41.5% in the lower tidal volume ventilation with $ECCO_2R$ group *vs.* 39.5% in the standard care group (Risk Ratio, 1.05 (95% CI, 0.83–1.33); difference, 2.0% (95% CI, –7.6% to 11.5%); $p = 0.68$). This was unchanged after adjusting for age, Sequential Organ Failure Assessment (SOFA) score, and baseline PaO_2/FiO_2. Higher rates of adverse events were observed in the intervention arm: 168 (52% of patients) *vs.* 61 (23% of patients), including higher rates of intracranial hemorrhage and infectious complications.

Moreover, several issues may have affected the outcome in the $ECCO_2R$ group. In fact, in the intervention arm of the trial, there were higher rates of mandatory modes of mechanical ventilation and neuromuscular blockade and less use of prone positioning than in the control arm. In addition, several participating centers had little experience with the clinical application of $ECCO_2R$. Furthermore, although driving pressure in the $ECCO_2R$ group was 2–3 cmH_2O lower than in controls, with the expected significant decrease of mechanical load, in both groups, driving pressure was maintained below 14 cmH_2O, which has been suggested as a protective threshold to minimize VILI [69]. Future studies will need to investigate whether targeting a lower respiratory rate by study design with $ECCO_2R$ results in improved outcomes, as demonstrated in an elegant experimental large animal model [70].

Overall, the data presented in this study confirmed that achieving lower tidal volumes using $ECCO_2R$ is possible and highlighted how translating this physiologic effect into clinical benefit is challenging due to the complex and not fully revealed pathophysiology of VILI.

Other relevant studies on $ECCO_2R$ in ARDS are summarized in Table 1.

TABLE 1. Relevant studies of $ECCO_2R$ in ARDS.

Study	No. of patients	$ECCO_2R$ Characteristics				Time on $ECCO_2R$	Major Results
		Configuration	Blood flow (mL/min)	Sweep flow (L/min)	Membrane (material); surface in m^2		
Terragni *et al.* [77]	32	RRT platform adapted to $ECCO_2R$ and a double lumen catheter (femoral)	191–422	8	PLP* (Decap®, Hemodec, Salerno, Italy); 0.33	6 (3.5–7) d	Prospective study. IMV + LPV to maintain P_{PLAT} 28–30 cmH_2O After 72 h of IMV, $ECCO_2R$ started with posterior decreasing of V_T. V_T successfully decreased to 4 mL/kg PBW and P_{PLAT} decreased to 25.0 cmH_2O ($p < 0.001$). $ECCO_2R$ prevented respiratory acidosis. Reduction of biomarkers of lung injury after 72 h of ultraprotective ventilation.
Bein *et al.* [68]	79	Femoral AV PECLA	1300	Not reported	PMP** (iLA AV, Novalung, Heil-bronn,Germany); 1.3	7.4 (3–11) d	Randomized controlled trial. AV-$ECCO_2R$ commencement after 24 h in moderate/severe ARDS. $ECCO_2R$ group aimed a V_T 3 mL/kg PBW. Control group aimed for a V_T 6 mL/kg PBW. No significant differences in VFDs at D-28 or D-60. $ECCO_2R$ + ARDS with P/F $\leq$150 had significantly shorter duration of ventilation at D-60. Significantly higher rate of bleeding in the $ECCO_2R$ group.
Fanelli *et al.* [56]	15	VV system and single double lumen catheter with femoral or jugular approach	435	10	PLP* based on siloxane layer (ALung Hemolung RAS); 0.59	2 h	Prospective study. Moderate/severe ARDS. V_T reduced to 4 mL/kg PBW. $ECCO_2R$ started after severe respiratory acidosis (pH $<$ 7.25 + $PaCO_2$ $>$ 60 mmHg). $ECCO_2R$ successfully reverted respiratory acidosis ECMO needed in 2 patients.
Augy *et al.* [78]	70	VV system and a double-lumen catheter	430	Not reported	PLP* based on siloxane layer (ALung Hemolung RAS) or PMP; 1.3 (Novalung iLA activve); 0.59	5 d	Multicenter, observational, prospective, cohort study. Ultraprotective ventilation for ARDS patients, rest of indications related to COPD patients. Significant reduction in V_T was observed in ARDS patients, up to 4 mL/kg PBW. Side effects related to the device: hemolysis, bleeding, and membrane clotting. 3 deaths related to $ECCO_2R$.
Schmidt *et al.* [79]	20	VV system managed with RRT platform via a 15.5-Fr single dual lumen catheter (femoral or jugular)	420	10	PMP** (Pris-maLung®; Gambro-Baxter); 0.32	31 h	Prospective multicenter study. Mild/moderate ARDS V_T progressively decreased to 4 mL/kg within 2 h + PEEP adjustment to aimed P_{PLAT} 23–25 cmH_2O using a RRT platform. No ECMO requirement. No worsening oxygenation. $ECCO_2R$ with RRT platform was feasible for ultraprotective ventilation.

TABLE 1. Continued.

Study	No. of patients	$ECCO_2R$ Characteristics				Time on $ECCO_2R$	Major Results
		Configuration	Blood flow (mL/min)	Sweep flow (L/min)	Membrane (material); surface in m^2		
Ding X *et al.* [80]	12	VV configuration with two 12-Fr two lumen hemodialysis into the right jugular vein and one of the femoral veins	342	10	PMP** (PrismaLung®; Gambro-Baxter); 0.32	Not reported	Single-center, prospective study. COVID-19 ARDS patients with refractory hypercapnia with compliance 13.29 $\pm$ 4.88 mL/cmH_2O. Low-flow $ECCO_2R$ system based on the RRT platform can reduce the $PaCO_2$ level <50 mmHg and significantly decrease the P_{PLAT}, driving pressure and mechanical power in moderate hypercapnic patients. Twenty-four hours later, the DP and P_{PLAT} slightly increased, but were still significantly reduced compared with the baseline.
Combes *et al.* [66]	95	VV configuration with a double-lumen catheter	300–500 *vs.* 800–1000	6–10	PLP* based on siloxane layer (ALung Hemolung RAS, iLA activve, Novalung, Cardiohelp® HLS 5.0, Getinge)	5 (3–8) d	Prospective multicenter international phase II study. Ultraprotective settings by 8 h and 24 h was achieved significantly in 78% at 8 h and 82% at 24 h of $ECCO_2R$ running. Two SAEs related to $ECCO_2R$ use (brain hemorrhage and pneumothorax). $ECCO_2R$- related AE were reported in 39% of the patients. Sixty-nine patients (73%) were alive at day 28. Fifty-nine patients (62%) were alive at hospital discharge.
McNamee JJ *et al.* [57]	405	VV configuration with a dual-lumen catheter inserted percutaneously into a central vein	350–450	10	PLP* based on siloxane layer (Alung Hemolung-RAS system); 0.59	4 d	Pragmatic, multi center, open label, randomized controlled and cost-effectiveness clinical trial. No difference in primary outcome of day 90 all-cause mortality 41.5% in the lower tidal volume ventilation with extracorporeal carbon dioxide removal group *vs.* 39.5% in the standard care group Risk Ratio, 1.05 (95% CI, 0.83–1.33); difference, 2.0% (95% CI, −7.6% to 11.5%); $p = 0.68$). Higher rates of adverse events: 168 (52% of patients) *vs.* 61 (23% of patients) 65 of these felt to be related to study intervention. Higher rates of intracranial hemorrhage: 10 *vs.* 25 were thought related to the intervention and 3 which resulted in death. Higher rates of infectious complications (7 *vs.* 1).

**PLP: polypropylene; **PMP: poly-4-methyl-1-pentene; AE: adverse effects; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; LPV: lung protective ventilation; PECLA: pumpless extracorporeal lung assist; PEEP: positive end-expiratory pressure; P_{PLAT}: Plateau pressure; RRT: renal replacement therapy; V_T: tidal volume; SAE: serious adverse effects; IMV: invasive mechanical ventilation; PBW: predicted body weight; AV: arterio-venous; iLA: interventional lung assist; VFDs: ventilator free days; VV: veno-venous; RAS: Respiratory Assist System; HLS: Heart-Lung Support; ECMO: extracorporeal membrane oxygenation; DP: driving pressure.*

5. Complications

Although $ECCO_2R$ seems to improve or correct hypercapnic acidosis, its use is associated with a range of vascular, hematological, and other complications (Table 2). In a recent international feasibility trial, $ECCO_2R$-related adverse events such as catheter displacement or infectious complications were observed in 2% and membrane lung clotting or bleeding in 14% of patients, highlighting the coagulation/anticoagulation balance as a key issue [56].

TABLE 2. Complications associated with $ECCO_2R$.

Therapy-related
• Worsening of hypoxemia at the onset of low tidal ventilation
• Bleeding (pulmonary, gastrointestinal, cerebral)
• Hemolysis
• Consumption coagulopathy
• Thrombocytopenia/thrombopathy
• Air embolism
Catheter-related
• Vascular injury (bleeding)
• Catheter infection
• Thrombosis
• Hematoma, aneurism, pseudoaneurysm
• Distal limb ischemia (AV-$ECCO_2R$)
• Catheter malposition, dislodgement or kinking
• Compartment syndrome
• Accidental arterial insertion (AV-$ECCO_2R$ system)
• Recirculation
Device-related
• Pump malfunction
• Oxygenator malfunction
• Heat exchanger failure
• Clot plugging

AV-$ECCO_2R$: arterio-venous extracorporeal carbon dioxide removal.

$ECCO_2R$ can worsen hypoxemia and increase FiO_2 requirements due to derecruitment, which can be counteracted by applying higher levels of PEEP. Lower partial alveolar oxygen pressure can also result from a reduced lung respiratory quotient [71–73].

One of the most important differences between AV and VV configurations is the risk of complications related to the femoral artery catheterization with partial obstruction of blood flow and the potential occurrence of limb ischemia.

Hemorrhagic events related to vascular access and anticoagulation are the most frequent complications of $ECCO_2R$. The low flow makes systemic anticoagulation necessary, increasing significant bleeding risk, including cerebral, gastrointestinal, and nasopharyngeal bleeding. The contact between blood and the artificial surfaces of the circuit at very low flows can lead to a secondary consumption of clotting factors and associated bleeding complications. Clinically significant hemorrhagic complications are reported in the range between 2% and 50% [65, 74].

Although most systems are also coated with heparin to minimize thrombogenicity of the surface as little as possible, thrombus formation may build-up due to increased exposure time of the blood in contact with the artificial membrane lung and circuit due to lower flow rates. Clotting in the system may reduce or compromise the membrane efficiency or completely obstruct the circuit if anticoagulation is not achieved. This may reduce the membrane efficiency and consequently increase CO_2 levels rapidly. Membrane thrombosis must be considered a life-threatening event, requiring the immediate substitution of the circuit.

Heparin-induced thrombocytopenia is rarely observed. In this case, an albumin or phosphorylcholine/phosphatidylcholine coating can be requested [75].

The careful choice of adequate vascular access is critical in preventing thrombosis and detecting catheter kinking, precluding the achievement of target blood flow rates [56]. Catheter displacement or kinking may also result in pump malfunction and membrane thrombosis. Hence, subclavian or jugular vein cannulation is preferred over the femoral vein access when a high body mass index or intraabdominal hypertension is present. Intravascular hemolysis also has been reported.

6. Future perspectives

$ECCO_2R$ effectively allows the implementation of protective or ultra-protective ventilation in patients with ARDS. However, current data do not demonstrate efficacy in improving patient-centered outcomes. Further investigations, warranted to establish the overall clinical effect of $ECCO_2R$ in patients with ARDS, will need to address several important issues regarding, among others, the definition of optimal blood flow and hence circuit configuration, the definition of optimal target of pH, CO_2, tidal volumes and alveolar distending pressures, and the definition of optimal anticoagulation strategies. These advancements will also clarify whether $ECCO_2R$ should be applied in all patients with ARDS, only in specific subphenotypes, or whether a personalized mechanical ventilation strategy, including $ECCO_2R$, should be delivered to each patient based on specific disease characteristics and risk factors.

7. Summary and recommendations

$ECCO_2R$ may be a promising adjuvant therapeutic strategy to reduce the injury induced by mechanical ventilation.

In a recent European consensus on using $ECCO_2R$ for ultraprotective ventilation in ARDS patients, driving pressure with plateau pressure optimization was the main criteria for commencement of the technique. The clinical targets were pH $>$7.30, respiratory rate $<$20–25 breaths/min, P_{PLAT} $<$25 cmH_2O and driving pressure $<$14 cmH_2O [76]. At the moment, $ECCO_2R$ in patients with ARDS should not be used in patients outside clinical trials.

Future studies that harness the potential benefits of $ECCO_2R$

without increasing the risk of other complications are needed to progress this technology.

AUTHOR CONTRIBUTIONS

LMQ and LDS—designed the study, wrote original draft, reviewed and edited. LDS and JM—reviewed, edited and corrected English. JM—supervised and reviewed.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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