Review

Recent advances and future directions in Extracorporeal Carbon Dioxide Removal

Tomás Lamas *, Susana M. Fernandes, Francesco Vasques, Christian Karagiannidis, Luigi Camporota, Nicholas Barret

Posted Date: 28 November 2024

doi: 10.20944/preprints202411.2299.v1

Keywords: extra-corporeal CO2 Removal (ECCO2R); acute respiratory distress syndrome (ARDS); Haemolysis; thrombosis

Review

Recent Advances and Future Directions in Extracorporeal Carbon Dioxide Removal

Tomás Lamas [1,2*], Susana Fernandes [3,4], Christian Karagiannidis [5], Francesco Vasques [6,7], Luigi Camporota [6,7] and Nicholas Barrett [6]

1 ICU Department at Hospital Egas, Lisbon, Portugal
2 ICU Department at CUF Tejo, Lisbon, Portugal
3 Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
4 Serviço de Medicina Intensiva, ULS Santa Maria, Lisbon, Portugal
5 Department of Pneumology and Critical Care Medicine, ARDS and ECMO Centre, Cologne-Merheim Hospital, Cologne, Germany
6 Department of Adult Critical Care, Guy´s and St Thomas´ NHS Foundation Trust, King´s Health Partners, London, UK
7 Division of Centre of Human Applied Physiological Sciences, King's College London, London, UK
* Correspondence: tomaslamas2009@gmail.com

Abstract: Extracorporeal carbon dioxide removal ($ECCO_2R$) is an emerging technique designed to reduce carbon dioxide (CO_2) levels in venous blood while enabling lung-protective ventilation or alleviating the work of breathing. Unlike high-flow extracorporeal membrane oxygenation (ECMO), $ECCO_2R$ operates at lower blood flows (0.4–1.5 L/min), making it less invasive, with smaller cannulas and simpler devices. Despite encouraging results in controlling respiratory acidosis, its broader adoption is hindered by complications, including haemolysis, thrombosis, and bleeding.Technological advances, including enhanced membrane design, gas exchange efficiency, and anticoagulation strategies, are essential to improving safety and efficacy. Innovations such as wearable prototypes that adapt CO_2 removal to patient activity and catheter-based systems for lower blood flow are expanding the potential applications of $ECCO_2R$, including as a bridge to lung transplantation and in outpatient settings. Promising experimental approaches include respiratory dialysis, carbonic anhydrase-coated membranes, and electrodialysis to maximise CO_2 removal.Further research is needed to optimise device performance, develop cost-effective systems, and establish standardised protocols for safe clinical implementation. As the technology matures, integration with artificial intelligence (AI) and machine learning may personalise therapy, improving outcomes. Ongoing clinical trials will be pivotal in addressing these challenges, ultimately enhancing the role of $ECCO_2R$ in critical care and its accessibility across healthcare settings.

Keywords: extra-corporeal CO2 Removal (ECCO2R) 1; acute respiratory distress syndrome (ARDS) 2; Haemolysis 3; thrombosis 4

1. Introduction

Extracorporeal carbon dioxide removal ($ECCO_2R$) is a technique designed to remove carbon dioxide from the venous blood, thereby reducing the intensity of mechanical ventilation. Unlike high-flow extracorporeal membrane oxygenation (ECMO), $ECCO_2R$ does not provide oxygenation, as it operates at lower blood flows ranging from 0.4 up to 1.5 L/min, depending on the device. The lower blood flow reduces the procedure's invasiveness, allowing smaller cannulae and simpler extracorporeal devices. To refine this lung-support technology, various $ECCO_2R$ configurations and techniques have been explored in benchtop and animal models.

There is a specific interest in using $ECCO_2R$ to improve the management of acute respiratory distress syndrome (ARDS) and chronic obstructive pulmonary disease (COPD). $ECCO_2R$ shows potential for other applications, including serving as a bridge to lung transplantation and enabling long-term CO_2 management in outpatient settings. ECCO2R faces barriers such as hemolysis,

 doi:10.20944/preprints202411.2299.v1

thrombosis and bleeding, which limit its clinical adoption. This review highlights recent advancements in ECCO$_2$R technology, including device configurations, CO_2 removal efficiency, and optimised anticoagulation strategies. We explore the physiological impacts of ECCO$_2$R systems studied through animal models and mock circulation setups to evaluate safety and performance. We also explore key research priorities, including improving gas exchange membranes, refining blood flow and anticoagulation protocols to reduce complications, and investigating innovative approaches such as membrane acidification and hybrid devices.

2. Clinical Evidence for ECCO$_2$R

ECCO$_2$R has been investigated for its role in managing acute respiratory distress syndrome (ARDS) and acute hypercapnic respiratory failure, particularly acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The earliest model of ECCO$_2$R utilised a pumpless arterio-venous (AV) approach, diverting a portion of the patient's cardiac output through the device [1] via a femoral arterio-venous circuit. Several case reports and case series documented the use of pumpless AV ECCO$_2$R [2–12] and demonstrated their ability to decrease arterial CO_2 and resolve respiratory acidosis. However, complications associated with the use of AV ECCO$_2$R were considerable, including bleeding (18-47%), thrombosis (0-20%) and limb ischaemia (4.5-22%)[2,4].

Pumped ECCO$_2$R systems were later developed, enabling a veno-venous (VV) approach, typically using a double-lumen cannula placed in the femoral or jugular vein[13]. Animal studies consistently show that VV ECCO$_2$R can effectively control respiratory acidosis [14–18]. Similarly, uncontrolled clinical studies demonstrated similar results in patients with ARDS and AECOPD[4,16,19–24]. However, a retrospective propensity-matched case-control study using VV ECCO$_2$R in COPD found no difference in outcome with ECCO$_2$R use [25]. Recently, VV ECCO$_2$R has been safely integrated with renal replacement therapy platforms in patients with acute respiratory distress syndrome [26,27] and AECOPD [28]. Case series have also reported reduced intubation rate in AECOPD and decreased respiratory rate when used alone or with non-invasive mechanical ventilation[29–31].

In ARDS management, the delivery of lung protective ventilation - reducing driving pressure, optimising PEEP, limiting plateau pressure and tidal volume – is hindered by significant respiratory acidosis and acute cor pulmonale. Trials, such as the SUPERNOVA study, investigated using ECCO$_2$R to achieve ultra-low tidal volumes of 3-4 mL/kg in mechanically ventilated ARDS patients, demonstrating feasibility and safety in controlling arterial CO2 [26]. The UK-based REST trial, the first randomised controlled trial in this area, compared standard tidal volume ventilation (6-8 mL/kg) to ultra-low tidal volume ventilation (3-4 mL/kg) using ECCO$_2$R. While the trial achieved significant separation between groups in tidal volume and maintained comparable PaCO2 and pH, it showed no difference in 90-day mortality. The ECCO$_2$R group experienced significantly higher complication rates, including bleeding with intracranial haemorrhage, leading to early trial termination [32].

For AECOPD, non-invasive ventilation (NIV) remains the gold standard. However, ECCO$_2$R has been explored as an option for patients who fail or cannot tolerate NIV. Trials have shown faster resolution of respiratory acidosis and work of breathing with ECCO$_2$R, though they were not powered to assess mortality. Other studies have evaluated ECCO$_2$R for preventing intubation or enabling early extubation, finding no differences in ventilator-free days or mortality, with higher mortality in the NIV group when ECCO$_2$R was added[33].

Despite mixed results, interest in ECCO$_2$R persists, particularly regarding the optimal blood flow rate for clinical benefit. Evidence suggests that higher-flow devices (500–1,000 mL/min) provide superior CO_2 clearance compared to lower-flow systems (<500 mL/min)[34,35]. All the RCTs to date have used devices with a maximum blood flow below 500mL/minute. Future trials should investigate the potential of higher blood flow ECCO$_2$R devices to improve clinical outcomes.

3. Key Areas of Future Research

The future of ECCO$_2$R remains challenging due to the clinical outcomes observed so far and the significant complications associated with current devices. Priority should be given to addressing

 doi:10.20944/preprints202411.2299.v1

technical issues such as haemolysis, thrombosis, and bleeding. Research must also define optimal parameters for blood flow, sweep gas efficiency, and monitoring while developing methods to compare different devices for practical application. Experimental studies using appropriate circuits and biological models are essential to translate findings into clinical practice. Ultimately, well-designed clinical trials addressing patient-centred outcomes will be crucial in determining this technology's role in critically ill patients.

3.1 Hemolysis

Hemolysis is a significant complication of extracorporeal support and is independently associated with mortality [36,36,37]. A key contributor to hemolysis is shear stress caused by blood circulating through artificial circuits. This shear rate and stress arise from artificial surfaces and continuous flow patterns [38]. Factors such as catheter size and type, flow rates, pump design (roller or centrifugal), lung membrane characteristics, anticoagulation methods (coating and systemic), and $ECCO_2R$ settings all influence haemolysis rates and system performance.

Haemolysis is best detected by measuring plasma free Hb (PFHb), the most reliable marker of RBC injury and breakdown [39,40]. Evidence suggests that haemolysis increases non-linearly with reducing blood flows, as prolonged exposure to artificial surfaces amplifies the effective stress on blood components [41,34].

When the haemoglobin scavenging capacity of haptoglobin is exceeded, free haemoglobin dimers circulate in the bloodstream, releasing free heme [42]. This free haemoglobin depletes nitric oxide (NO) by converting it into nitrate, impairing NO's regulatory role in vascular smooth muscle tone. The resulting NO depletion leads to potent vasoconstriction and increased systemic and pulmonary vascular resistance [43,44,45]. Additionally, NO depletion disrupts platelet and endothelial function, enhancing platelet aggregation and thrombus formation mediated by the von Willebrand factor [46,47,48].

Free haemoglobin initiates a cycle of inflammation that culminates in a procoagulant state and thrombus formation. This process exacerbates haemolysis, depletes clotting factors, and leads to thrombocytopenia and impaired platelet function [49], which may result in an acquired von Willebrand syndrome [50,51].

To address this frequent complication, we require improved devices and a greater clinical understanding of how device usage impacts haemolysis.

3.2 Thrombosis and Bleeding

Anticoagulation is a critical concern in extracorporeal circulation technology, given that anticoagulation and the impact of shear stress on coagulation proteins may lead to increased bleeding risk [21,32,52–56]. On the other hand, thrombosis is responsible for locally impaired flow conditions in cannulas, pumps and membrane lungs, which lead to mechanical stress and hemolysis. The coagulation cascade is activated when whole blood comes into contact with an artificial surface, exacerbated by slow blood flow. Relative slow blood flow occurs in low-shear circuit parts, such as tubing connectors, with increased thrombin generation[57,58] and minimal clot initiators required to trigger clot formation [59]. The artificial membrane oxygenator and the centrifugal head pump are the two main circuit components affected by higher mechanical stress and risk of thrombus formation. Centrifugal head pump thrombosis is usually associated with acute and severe hemolysis [37]. Membrane thrombosis reduces gas exchange impacting device efficiency.

 doi:10.20944/preprints202411.2299.v1

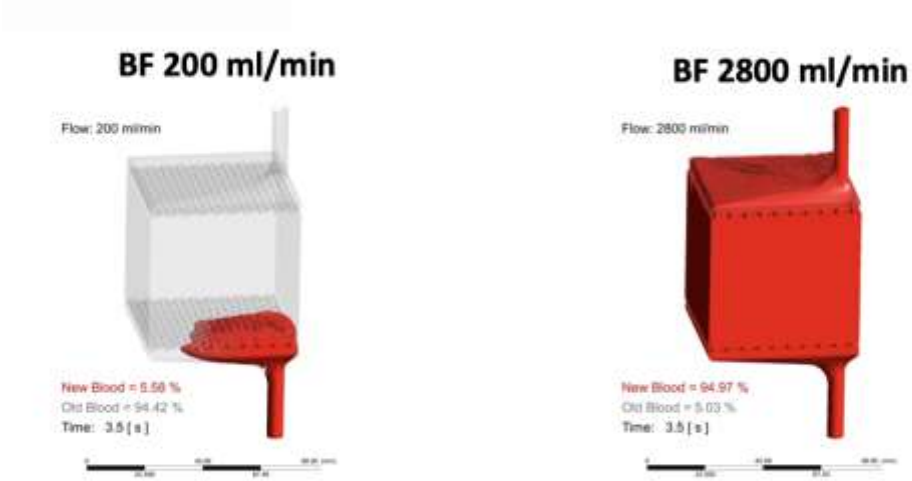

Figure 1. Example of different blood washouts depending on high and low blood flows in membrane oxygenator with impact on anticoagulation requirements to prevent membrane clotting. Pictures kindly provided by F. Hesselmann and R. Borchardt, Aachen, Germany.

Contrary to expectations, low blood flow rates (1–1.5 L/min) are associated with a significantly higher risk of haemolysis (3.2 to 6.6 times greater Haemolysis Index) compared to higher blood flow (4 L/min). In low-flow systems (<1.5 L/min), citrate anticoagulation has been shown to outperform heparin by causing less haemolysis and platelet loss [60]. Citrate better preserves red blood cell density, membrane stability, and deformability, reducing haemolysis over three days of storage [61]. In animal studies, Cardenas et al. demonstrated no thrombus formation and hemolysis at different low flow levels (500ml/min, 800ml/min, 1000ml/min) using citrate anticoagulation in 24 hours. Although higher blood flows may reduce calcium chelation efficiency due to elevated ionised calcium levels, this did not correlate with thrombus formation. When comparing citrate to heparin anticoagulation at electronic microscopy, analysis of membrane oxygenator fibres revealed cellular and fibrin adhesion on heparin anticoagulation even after 6 hours of anticoagulation [62]. Despite these theoretical advantages, heparin remains the most commonly used anticoagulant in clinical ECCO$_2$R due to concerns about citrate toxicity.

A significant complication of citrate anticoagulation in animal studies was progressive hypocalcaemia, even with calcium supplementation, due to the absence of a hemofilter to remove excess citrate. This increased systemic citrate load, heightening the risk of citrate toxicity [62–64]. Further research is needed to enhance the safety profile of citrate anticoagulation for clinical ECCO$_2$R.

An emerging alternative to sodium citrate is citric acid anticoagulation, which provides a triple effect: calcium chelation, platelet inhibition, and a regional anticoagulant effect from an acidic environment [70]. Citric acid has also enhanced CO_2 removal by blood acidification at the artificial membrane [65]. However, hepatic clearance of citrate in humans is limited [66], which reduces the maximum blood flow of ECCO$_2$R to 150ml/min, which can be offset by an increase in CO_2 removal efficiency driven by the acidification of the blood [67–70].

Other alternatives to heparin, such as nafamostat mesylate, bivalirudin, and argatroban, are being considered, especially for patients at high risk of bleeding or heparin-induced thrombocytopenia (HITT). These alternatives offer advantages regarding bleeding risks and drug monitoring but are limited by high costs and short half-lives.

4. CO_2 Removal Rate Performance

4.1 Cannula

ECCO$_2$R typically employs smaller cannulas (13–14 Fr) than the larger cannulas used in higher-flow ECMO. Venous access is generally achieved via the right internal jugular or femoral veins, with

 doi:10.20944/preprints202411.2299.v1

vessel puncture performed under ultrasound guidance. While the smaller cannulas offer advantages such as reduced invasiveness, their use presents several challenges that can impact both efficacy and patient safety. A key issue is maintaining adequate blood flow through the smaller cannulas. A smaller diameter cannula with higher flow rates increases shear stress, which may reduce CO_2 removal efficiency due to insufficient flow, ultimately limiting the therapy's effectiveness. Multiple single-lumen catheters can replace double-lumen catheters. This involves using separate access points in the jugular and femoral veins to achieve uninterrupted blood flow of approximately 450 mL/min with minimal recirculation [71]. Another relevant factor for $ECCO_2R$ efficiency is the minimisation of blood recirculation related to catheters. Catheter recirculation was related to catheter type and brand, site of placement, catheter length, time on dialysis, and time on the current catheter and was measured via ultrasound dilution technique [72]. Catheters placed in the internal jugular or subclavian veins, with the tip near the right atrium, minimise recirculation, making them more effective for $ECCO_2R$. In contrast, femoral catheters have higher recirculation rates and are less suitable for this therapy.

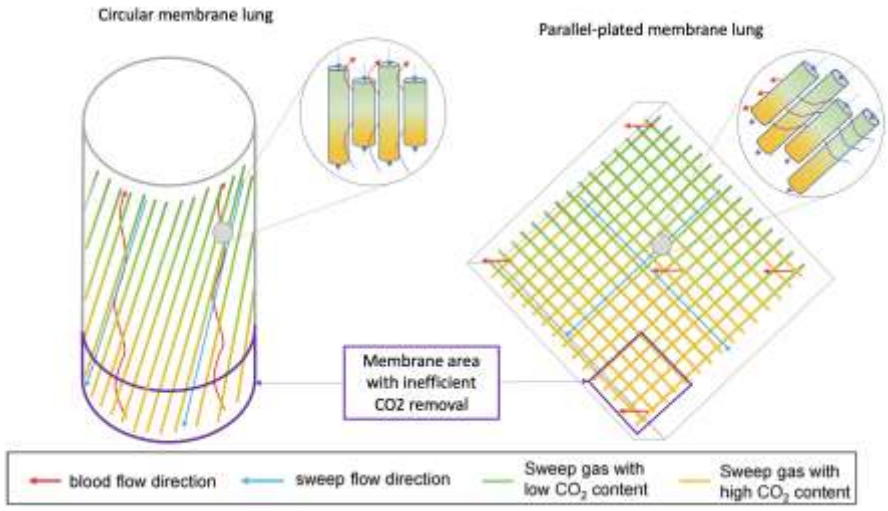

Figure 2. Fiber arrangement in parallel plate and circular Membrane Lungs (ML).
In the circular ML, blood flow is nearly antiparallel to the gas fibres and flow. At the lower part of the ML, where blood enters, it encounters sweep gas with the highest CO_2 concentration. Since CO_2 removal depends on the diffusion gradient between the gas and blood—small in this region—CO_2 clearance is inefficient here. In the parallel-plate MLs, blood flows perpendicularly to the gas fibres. Similarly, at the lower part of the ML, where blood interacts with gas containing the highest CO_2 levels, CO_2 removal is less effective. With permission from Schwärzel et al. [73].

4.2 Pumps, Membranes and Circuits

4.2.1. Pumps

Conventionally, $ECCO_2R$ uses roller, centrifugal or diagonal, electric or electromagnetic pumps. The roller pumps used in $ECCO_2R$ systems were developed for renal replacement therapy (RRT) [74–76] or centrifugal pumps used for high-flow extracorporeal membrane oxygenation (ECMO) devices, with few systems explicitly designed for $ECCO_2R$ [14,29,77]. However, RRT devices driven by roller pumps are limited in blood flow rates (usually up to 500 mL/min), limiting the CO_2 removal performance. Standard ECMO centrifugal pumps running below 2L/min cause increasing shear stress, leading to haemolysis [41].

Potential new pump technologies are on the horizon, for example, an innovative membrane and pump integrated to operate at very low flow (250ml/min) using six rotating impellers inside a cylindrical membrane configuration with a total surface area of 0.42m2. Blood moves from inside to outside through membrane fibres, allowing up to 75ml/min CO_2 removal rate with a hemolysis level comparable to standard CO_2 removal devices [78].

 doi:10.20944/preprints202411.2299.v1

4.2.2. Membranes

Three major factors determine the amount of gas crossing membranes: the diffusion gradient, the membrane-blood contact time, and the characteristics of the membrane diffusion. The CO_2 diffusion gradient is determined by the CO_2 content of the blood and the air passing through the membrane lung, as well as the speed of the airflow. Membrane-blood contact time is determined by membrane geometry. Modern membrane lungs achieve adequate gas exchange with 1 to 3 m2 surface areas (Table 1).

Table 1. Comparison of available ECCO2R in the market based on the pump (pumpless, roller and centrifugal) and membrane function (gas and/or fluid CO_2 removal). The table summarises the key characteristics of roller and centrifugal pumps, focusing on parameters such as blood flow limits, priming volume, membrane surface area, membrane material, CO_2 extraction efficiency, VCO_2 monitor and circuit life. [19,27,79–83]

Pump type	Pumpless	Roller								Centrifugal			
Membrane function	Gas CO2 removal	Gas CO2 removal	Gas CO2 removal / Hemofilter						CO2 Fluid Removal	Gas CO2 removal			
Blood flow (mL/min)	500-4500	100-450	30-450	200-400			200-800	200-500	100-400	350-500	500-1000	100-7.000	2.500-7.000
Vascular access	Arterio-venous	Veno-Venous											
Cannula size	15Fr	13-14Fr	13Fr	13.5Fr	13.5Fr	13.5Fr	15.5Fr	13.5Fr	13-14Fr	13.5Fr	18-19Fr	18-26Fr	Drainage: 25-29Fr Reinjection: 17-21Fr
Cannula configuration	Arterial and venous	Double lumen	Double-lumen	Double-lumen	Double-lumen	Double-lumen	Double-lumen	Double-lumen	Double lumen	Double-lumen	Single or Double-lumen	Single or double lumen	
Priming volume	175	220	200-500	140-160	155-190	100	180	180	200ml (albumin)	200-300	250-350	605	800-900
Membrane position related to hemofilter	X	X	Pre	Post	Post	Post	Pre	Pre	X	X	X	X	X
Membrane surface (m2)	1.3	1.8	0.33-1.31	0.32	0.8	1.31	1.8	1.8	none	0.59	0.65	1.9	1.8
Membrane/coating	PMP	PMP/PC	PMP	PMP/Hep	PMP/PC	PMP/PC	PMP/PC	PMP/PC	(n.a.)	PMP/Silo+Hep	PMP	PMP	PMP/PC
CO2 extraction (% of initial value)	50-60	20-35	n.a.	<25		70-80	70-78	80-90	25-50	25	50	>50	>50
VCO2 Monitor	No	Yes	No	No	No	No	Yes	No	No	Yes	No	No	No
Validated circuit life		5 days (n.a.)	5 days (n.a.)	3 days (n.a.)	3 days (1800€)	3 days (1800€)	5 days (2100€)	3 days (1800€)	24h (n.a.)	7 days (n.a.)	(n.a.)	30 days	30 days
Brand	ILA Activve® Novalung	Prolung®	Decap Smart B. Braun (previously Hemodec)	Prismalung membrane, Baxter®	Prismalung Plus membrane, Baxter	miniECCO2R Evolution membrane, Fresenius®	CO2 Hover, Eurosets®	miniECCO2R Eurosets membrane, B. Braun	ADVOS®®	ALung Hemolung RAS®	MiniLung® Novalung	XLung® Novalung	Maquet Cardiohelp®

4.2.2.1 Materials

Early fibres were constructed with microporous polypropylene. Micropores create microscopic blood-gas interfaces, allowing efficient gas exchange and causing plasma leaks. Recently, non-microporous poly-4-methyl-1-pentene (PMP) has been used; it provides superior gas exchange, better biocompatibility, and is less susceptible to plasma leak [84–86]. The gas exchange has been improved by arranging fibres into a complex mat and running blood on the outside[87]. This arrangement allows perpendicular blood flow to the fibres, enhancing mass transfer by reducing the diffusion path length compared to parallel flow.

4.2.2.2 Novel Surfaces for ECCO2R

New materials and surface coatings are designed to reduce the inflammatory and coagulation responses triggered by artificial surfaces. Bioactive coatings, such as heparin-based and nitric oxide (NO) releasing materials, mimic natural endothelium and prevent blood clotting. Membranes may include a nitric oxide (NO)-eluting NO-eluting ECCO2R system, tubing with NO-catalyzing surface coating or NO gas (80ppm) delivered into the membrane that inhibits platelet activation and aggregation to minimise thrombosis during extracorporeal CO_2 removal (ECCO2R) [88].

Endothelialisation of surfaces is an emerging approach, with efforts to create artificial materials that mimic the human endothelial layer, potentially reducing the need for systemic anticoagulation and preventing thrombosis. Further innovations focus on developing fully biocompatible materials to avoid bleeding and clotting complications without compromising oxygenation efficiency, raising the possibility for long-term respiratory support in chronic lung failure[89]. These include bioactive hollow fibre membranes (HFMs) coated with carbonic anhydrase (CA). CA immobilisation on HFMs

 doi:10.20944/preprints202411.2299.v1

increases the conversion of bicarbonate into CO_2, improving removal efficiency by creating a steeper diffusion gradient at the membrane surface. The CA-coated membranes also improved hemocompatibility, reducing platelet adhesion by 95% [90]. Acidic sweep gas containing sulfur dioxide (SO_2), in combination with carbonic anhydrase (CA) coated hollow fibre membranes (HFMs), can significantly enhance CO_2 removal from blood. This technique offers the potential for developing more efficient ECCO$_2$R devices. The findings could lead to smaller, less invasive respiratory support systems for patients with acute respiratory failure. [91].

Innovative therapies, such as intravascular gas exchange devices, hold promise for lung support in acute respiratory conditions both in and outside the hospital. They also have long-term potential for managing chronic lung diseases while preserving patient mobility through continuous ECCO$_2$R. Despite their appeal, this technology has yet to reach clinical use. Only one device, the IVOX catheter, has advanced to human clinical trials but has yet to receive FDA approval. Technical challenges have hindered their progress, including optimising gas exchange within the vascular space and ensuring safety. Advancements in design may eventually offer a less invasive alternative to ECMO for managing acute respiratory failure [92].

4.2.2.3 Measuring device VCO_2 to assess membrane performance

When comparing devices and evaluating efficiency, it is crucial to understand how CO_2 is measured to estimate carbon dioxide transfer across the artificial membrane. This can be done by assessing trans-membrane CO_2 content differences using whole blood CO_2 content using the Douglas equation [93] or measuring the partial pressure of CO_2 in the effluent gas using infrared CO_2 sensors.[94] In both approaches, normalising to a standardised inlet PCO_2 is essential to define the device's operating range and enable meaningful efficiency comparisons.

One of the concerns with effluent gas VCO_2 measurement is the need for more independent validation of VCO_2. However, this has been done with one device, little is known about the accuracy of the devices in which VCO_2 is measured with an infrared sensor measurement (Table 1)[95,96]. To improve comparative evaluations, the VCO_2 of each membrane and device should be standardised to inlet CO_2 and blood flow for consistent comparison and performance assessment. Manufacturers should ideally report their device's index as VCO_2 per membrane surface area (e.g., ml/min/m^2).[78]

4.3. Combined CO_2 Removal ("Lung Dialysis") with renal support

Other strategies for enhancing CO_2 removal from the blood focus on methods targeting bicarbonate, as around 90% of CO_2 in the blood is transported as bicarbonate (Figure 2). The gas exchange membrane can be isolated or combined with a "renal" membrane (hemofilter) to achieve this. Research has shown that combining extracorporeal CO_2 removal (ECCO$_2$R) with CRRT effectively reduces arterial CO_2 ($PaCO_2$), improves pH, and stabilises hemodynamics in patients with acute respiratory distress syndrome (ARDS) and renal failure. Despite these benefits, mortality rates in critically ill patients remain high, especially in the most severe cases [97]. Integrating a hollow-fibre gas exchanger into CRRT platforms is relatively simple, and the gas exchange membrane can be placed before or after the haemofilter. Some data suggest that the CO_2 removal rate tends to be higher when the membrane is before the hemofilter. However, the clinical impact of this remains unknown [74]. An alternative strategy is integrating gas and fluid fibres in parallel using a shared circuit [98].

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 November 2024 doi:10.20944/preprints202411.2299.v1

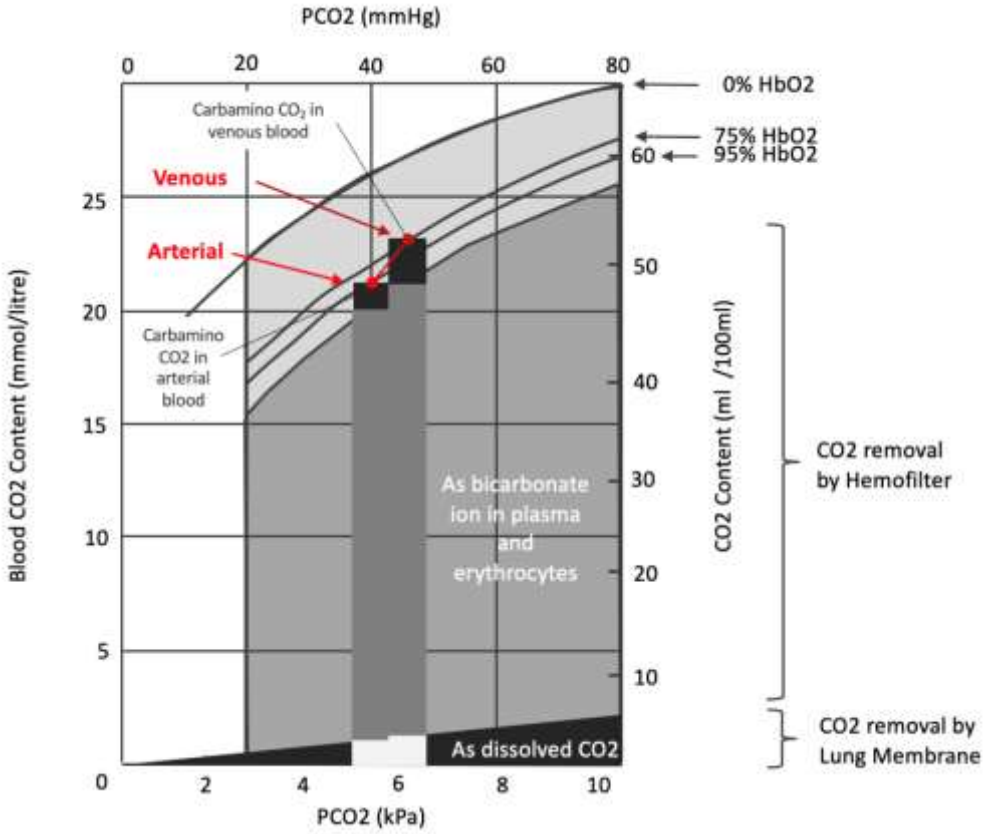

Figure 2. The proportion of carbamino form contribution from arterial CO_2 content to venous CO2 content is significantly higher than the other forms of CO_2 content due to the Haldane effect (increasing Hemoglobin affinity to CO_2 in lower oxygen concentration). The CO_2 removal of the gaseous phase of CO_2 represents only a small fraction of total CO_2 content. The bicarbonate removal using zero bicarbonate dialytic solution through hemofilter could contribute to significantly higher CO_2 removal of total CO_2 content, however, the blood buffer must be replaced by other natural buffers to maintain the acid-base equilibrium.

The optimal dialysis solution to use in combined devices remains to be discovered. Commonly available bicarbonate-based solutions increase total blood CO_2 content, which is problematic when high dialysis rates are required for solute clearance. Alternative solutions allow the simultaneous removal of H^+ and bicarbonate, maintaining acid-base balance whilst allowing CO_2 removal rates of up to 160 mL/min [99]. Several approaches seek to manipulate regional pH to alter bicarbonate or CO2 clearance. Alkalinisation with bicarbonate free solutions, enhance bicarbonate removal are being investigated in animal models [100]. However, these methods may prove impractical for clinical use due to acid-base derangements, hemolysis, cardiac arrhythmias, and depletion of micronutrients, even though several approaches to replace bicarbonate have been attempted [100,101]. Respiratory electrodialysis, which increases CO_2 partial pressure in the blood through regional acidification, has been shown to remove approximately 50% of the total CO_2 metabolic production, offering a promising strategy for efficient CO_2 removal. These varied strategies illustrate ongoing efforts to develop more effective means of extracorporeal CO_2 removal, particularly for critically ill patients with multiple organ failure [102].

5. Conclusions

The future of ECCO2R holds significant promise. However, two actions need to occur in parallel. First, the technology needs to be improved to reduce the impact on blood and coagulation whilst simultaneously increasing the efficiency of CO_2 removal. Second, the population who may benefit

and the timing of $ECCO_2R$ need to be better defined. $ECCO_2R$ is being evaluated for patients with ARDS and COPD, but other groups, including patients bridging to transplant, may benefit.

Advances in membrane technology and gas exchange efficiency could further reduce the size and blood flow requirements of $ECCO_2R$ systems, enhancing their safety and accessibility. These improvements could lead to the development of smaller, catheter-based systems that are less invasive and more practical for broader clinical use [100]. Developing new anticoagulation strategies for $ECCO_2R$ is crucial, given the delicate balance between preventing clot formation within the circuit and minimising the risk of bleeding complications in patients. Artificial intelligence (AI) and machine learning could act similarly to the respiratory centres, allowing automated changes in CO_2 clearance based on changes in blood CO_2 and pH [103]. Ultimately, miniaturisation, development of closed feedback loops, reduced impact on blood/coagulation, and efficiency improvements will benefit the ICU population and may also allow the development of wearable devices that act as destination or prolonged bridging therapies [104].

Clinical trials are ongoing and will determine $ECCO_2R$'s efficacy, safety, and best practices. Overall, $ECCO_2R$'s future looks bright, with ongoing innovation and research likely to expand its clinical applications and affect critical care practice.

Author Contributions: All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Ohtake S, Kawashima Y, Hirose H, et al. EXPERIMENTAL EVALUATION OF PUMPLESS ARTERIOVENOUS ECMO WITH POLYPROPYLENE HOLLOW FIBER MEMBRANE OXYGENATOR FOR PARTIAL RESPIRATORY SUPPORT. *ASAIO J*. 1983;29(1). https://journals.lww.com/asaiojournal/fulltext/1983/29000/experimental_evaluation_of_pumpless_arteriovenous.45.aspx.
2. Bein T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med*. 2006;34(5):1372-1377. doi:10.1097/01.CCM.0000215111.85483.BD
3. Bein T, Zimmermann M, Hergeth K, et al. Pumpless extracorporeal removal of carbon dioxide combined with ventilation using low tidal volume and high positive end-expiratory pressure in a patient with severe acute respiratory distress syndrome. *Anaesthesia*. 2009;64(2):195-198. doi:10.1111/J.1365-2044.2008.05735.X
4. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. *JAMA*. 1986;256(7):881-886.
5. Zimmermann M, Bein T, Arlt M, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care*. 2009;13(1). doi:10.1186/CC7703
6. Zimmermann M, Bein T, Philipp A, et al. Interhospital transportation of patients with severe lung failure on pumpless extracorporeal lung assist. *Br J Anaesth*. 2006;96(1):63-66. doi:10.1093/BJA/AEI274
7. Fischer S, Hoeper MM, Bein T, et al. Interventional lung assist: a new concept of protective ventilation in bridge to lung transplantation. *ASAIO J*. 2008;54(1):3-10. doi:10.1097/MAT.0B013E318161D6EC
8. Elliot SC, Paramasivam K, Oram J, Bodenham AR, Howell SJ, Mallick A. Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. *Crit Care Med*. 2007;35(3):945-948. doi:10.1097/01.CCM.0000257462.04514.15
9. Mallick A, Elliot S, Mckinlay J, Bodenham A. Extracorporeal carbon dioxide removal using the Novalung in a patient with intracranial bleeding. *Anaesthesia*. 2007;62(1):72-74. doi:10.1111/J.1365-2044.2006.04863.X
10. Zwischenberger JB, Alpard SK. Artificial lungs: a new inspiration. *Perfusion*. 2002;17(4):253-268. doi:10.1191/0267659102PF586OA
11. Zwischenberger JB, Alpard SK, Tao W, Deyo DJ, Bidani A. Percutaneous extracorporeal arteriovenous carbon dioxide removal improves survival in respiratory distress syndrome: a prospective randomized outcomes study in adult sheep. *J Thorac Cardiovasc Surg*. 2001;121(3):542-551. doi:10.1067/MTC.2001.112828
12. Zwischenberger JB, Savage C, Witt SA, Alpard SK, Harper DD, Deyo DJ. Arterio-venous CO2 removal (AVCO2R) perioperative management: rapid recovery and enhanced survival. *J Invest Surg*. 2002;15(1):15-21. doi:10.1080/08941930252807741
13. Terragni P, Maiolo G, Ranieri VM. Role and potentials of low-flow CO2 removal system in mechanical ventilation. *Curr Opin Crit Care*. 2012;18(1):93-98. doi:10.1097/MCC.0b013e32834f17ef

14. Batchinsky AI, Jordan BS, Regn D, et al. Respiratory dialysis: Reduction in dependence on mechanical ventilation by venovenous extracorporeal CO2 removal*. *Crit Care Med*. 2011;39(6):1382-1387. doi:10.1097/CCM.0b013e31820eda45
15. Ruberto F, Pugliese F, D'Alio A, et al. Extracorporeal removal CO2 using a venovenous, low-flow system (Decapsmart) in a lung transplanted patient: a case report. *Transplant Proc*. 2009;41(4):1412-1414. doi:10.1016/J.TRANSPROCEED.2009.03.048
16. Cardenas VJ, Lynch JE, Ates R, Miller L, Zwischenberger JB. Venovenous carbon dioxide removal in chronic obstructive pulmonary disease: experience in one patient. *ASAIO J*. 2009;55(4):420-422. doi:10.1097/MAT.0B013E3181A7B55D
17. Dorrington KL, McRae KM, Gardaz JP, Dunnill MS, Sykes MK, Wilkinson AR. A randomized comparison of total extracorporeal CO2 removal with conventional mechanical ventilation in experimental hyaline membrane disease. *Intensive Care Med*. 1989;15(3):184-191. doi:10.1007/BF01058571
18. Livigni S, Maio M, Ferretti E, et al. Efficacy and safety of a low-flow veno-venous carbon dioxide removal device: results of an experimental study in adult sheep. *Crit Care*. 2006;10(5). doi:10.1186/CC5082
19. Wearden PD, Federspiel WJ, Morley SW, et al. Respiratory dialysis with an active-mixing extracorporeal carbon dioxide removal system in a chronic sheep study. *Intensive Care Med*. 2012;38(10):1705-1711. doi:10.1007/S00134-012-2651-8
20. Garcia JP, Kon ZN, Evans C, et al. Ambulatory veno-venous extracorporeal membrane oxygenation: innovation and pitfalls. *J Thorac Cardiovasc Surg*. 2011;142(4):755-761. doi:10.1016/J.JTCVS.2011.07.029
21. Kluge S, Braune SA, Engel M, et al. Avoiding invasive mechanical ventilation by extracorporeal carbon dioxide removal in patients failing noninvasive ventilation. *Intensive Care Med*. 2012;38(10):1632-1639. doi:10.1007/S00134-012-2649-2
22. Extracorporeal lung support technologies - bridge to recovery and bridge to lung transplantation in adult patients: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2010;10(5):1-47.
23. Engel M, Albrecht H. Use of Extracorporeal CO2 Removal to Avoid Invasive Mechanical Ventilation in Hypercapnic Coma and Failure of Noninvasive Ventilation. *J Pulm Respir Med*. 2016;6(3). doi:10.4172/2161-105x.1000357
24. Hilty MP, Riva T, Cottini SR, Kleinert EM, Maggiorini A, Maggiorini M. Low flow veno-venous extracorporeal CO2 removal for acute hypercapnic respiratory failure. *Minerva Anestesiol*. 2017;83(8):812-823. doi:10.23736/S0375-9393.17.11524-5
25. Braune S, Sieweke A, Brettner F, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case-control study. *Intensive Care Med*. 2016;42(9):1437-1444. doi:10.1007/S00134-016-4452-Y
26. Combes A, Fanelli V, Pham T, et al. Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med*. 2019;45(5):592-600. doi:10.1007/S00134-019-05567-4
27. Husain-Syed F, Birk HW, Wilhelm J, et al. Extracorporeal Carbon Dioxide Removal Using a Renal Replacement Therapy Platform to Enhance Lung-Protective Ventilation in Hypercapnic Patients With Coronavirus Disease 2019-Associated Acute Respiratory Distress Syndrome. *Front Med*. 2020;7. doi:10.3389/FMED.2020.598379
28. Consales G, Zamidei L, Turani F, et al. Combined Renal-Pulmonary Extracorporeal Support with Low Blood Flow Techniques: A Retrospective Observational Study (CICERO Study). *Blood Purif*. 2022;51(4):299-308. doi:10.1159/000517280
29. Burki NK, Mani RK, Herth FJF, et al. A Novel Extracorporeal CO2 Removal System: Results of a Pilot Study of Hypercapnic Respiratory Failure in Patients With COPD. *Chest*. 2013;143(3):678. doi:10.1378/CHEST.12-0228
30. Spinelli E, Crotti S, Zacchetti L, et al. Effect of extracorporeal CO(2)removal on respiratory rate in spontaneously breathing patients with chronic obstructive pulmonary disease exacerbation. *Crit Care*. 2013;17(Suppl 2):P128. doi:10.1186/cc12066
31. Diehl JL, Piquilloud L, Vimpere D, et al. Physiological effects of adding ECCO2R to invasive mechanical ventilation for COPD exacerbations. *Ann Intensive Care*. 2020;10(1). doi:10.1186/S13613-020-00743-Y
32. McNamee JJ, Gillies MA, Barrett NA, et al. Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal vs Standard Care Ventilation on 90-Day Mortality in Patients With Acute Hypoxemic Respiratory Failure: The REST Randomized Clinical Trial. *JAMA*. 2021;326(11):1013-1023. doi:10.1001/JAMA.2021.13374
33. Tonetti T, Pisani L, Cavalli I, et al. Extracorporeal carbon dioxide removal for treatment of exacerbated chronic obstructive pulmonary disease (ORION): study protocol for a randomised controlled trial. *Trials*. 2021;22(1). doi:10.1186/S13063-021-05692-W
34. Karagiannidis C, Hesselmann F, Fan E. Physiological and Technical Considerations of Extracorporeal CO2 Removal. *Crit Care*. 2019;23(1). doi:10.1186/S13054-019-2367-Z

35. Karagiannidis C, Strassmann S, Brodie D, et al. Impact of membrane lung surface area and blood flow on extracorporeal CO2 removal during severe respiratory acidosis. *Intensive care Med Exp*. 2017;5(1). doi:10.1186/S40635-017-0147-0
36. Omar HR, Mirsaeidi M, Socias S, et al. Plasma free hemoglobin is an independent predictor of mortality among patients on extracorporeal membrane oxygenation support. *PLoS One*. 2015;10(4):1-10. doi:10.1371/journal.pone.0124034
37. Lehle K, Philipp A, Zeman F, et al. Technical-Induced Hemolysis in Patients with Respiratory Failure Supported with Veno-Venous ECMO - Prevalence and Risk Factors. *PLoS One*. 2015;10(11). doi:10.1371/JOURNAL.PONE.0143527
38. Nascimbene A, Neelamegham S, Frazier OH, Moake JL, Dong JF. Acquired von Willebrand syndrome associated with left ventricular assist device. *Blood*. 2016;127(25):3133-3141. doi:10.1182/BLOOD-2015-10-636480
39. Dufour N, Radjou A, Thuong M. Hemolysis and Plasma Free Hemoglobin During Extracorporeal Membrane Oxygenation Support: From Clinical Implications to Laboratory Details. *ASAIO J*. 2020;66(3):239-246. doi:10.1097/MAT.0000000000000974
40. Donadee C, Raat NJH, Kanias T, et al. Nitric oxide scavenging by red blood cell microparticles and cell-free hemoglobin as a mechanism for the red cell storage lesion. *Circulation*. 2011;124(4):465-476. doi:10.1161/CIRCULATIONAHA.110.008698
41. Gross-Hardt S, Hesselmann F, Arens J, et al. Low-flow assessment of current ECMO/ECCO2R rotary blood pumps and the potential effect on hemocompatibility. *Crit Care*. 2019;23(1). doi:10.1186/S13054-019-2622-3
42. Langlois MR, Delanghe JR. Biological and clinical significance of haptoglobin polymorphism in humans. *Clin Chem*. 1996;42(10):1589-1600. doi:10.1093/clinchem/42.10.1589
43. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293(13):1653-1662. doi:10.1001/JAMA.293.13.1653
44. Minneci PC, Deans KJ, Zhi H, et al. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest*. 2005;115(12):3409-3417. doi:10.1172/JCI25040
45. Schaer DJ, Buehler PW, Alayash AI, Belcher JD, Vercellotti GM. Hemolysis and free hemoglobin revisited: Exploring hemoglobin and hemin scavengers as a novel class of therapeutic proteins. *Blood*. 2013;121(8):1276-1284. doi:10.1182/blood-2012-11-451229
46. Da Q, Teruya M, Guchhait P, Teruya J, Olson JS, Cruz MA. Free hemoglobin increases von Willebrand factor-mediated platelet adhesion in vitro: implications for circulatory devices. *Blood*. 2015;126(20):2338-2341. doi:10.1182/BLOOD-2015-05-648030
47. L'Acqua C, Hod E. New perspectives on the thrombotic complications of haemolysis. *Br J Haematol*. 2015;168(2):175-185. doi:10.1111/BJH.13183
48. Wurzinger LJ, Blasberg P, Schmid-Schonbein H. Towards a concept of thrombosis in accelerated flow: rheology, fluid dynamics, and biochemistry. *Biorheology*. 1985;22(5):437-449. doi:10.3233/BIR-1985-22507
49. Oliver WC. Anticoagulation and coagulation management for ECMO. *Semin Cardiothorac Vasc Anesth*. 2009;13(3):154-175. doi:10.1177/1089253209347384
50. Malfertheiner M V., Pimenta LP, Von Bahr V, et al. Acquired von Willebrand syndrome in respiratory extracorporeal life support: a systematic review of the literature. *Crit Care Resusc*. 2017;19(Suppl 1):45-52. https://pubmed.ncbi.nlm.nih.gov/29084501/. Accessed September 25, 2024.
51. Kalbhenn J, Neuffer N, Zieger B, Schmutz A. Is Extracorporeal CO2 Removal Really "safe" and "less" Invasive? Observation of Blood Injury and Coagulation Impairment during ECCO2R. *ASAIO J*. 2017;63(5):666-671. doi:10.1097/MAT.0000000000000544
52. Burki NK, Mani RK, Herth FJF, et al. A Novel Extracorporeal CO 2 Removal System. *Chest*. 2013;143(3):678-686. doi:10.1378/chest.12-0228
53. Del Sorbo L, Fan E, Nava S, Ranieri VM. ECCO2R in COPD exacerbation only for the right patients and with the right strategy. *Intensive Care Med*. 2016;42(11):1830-1831. doi:10.1007/s00134-016-4493-2
54. Braune S, Sieweke A, Brettner F, et al. The feasibility and safety of extracorporeal carbon dioxide removal to avoid intubation in patients with COPD unresponsive to noninvasive ventilation for acute hypercapnic respiratory failure (ECLAIR study): multicentre case–control study. *Intensive Care Med*. 2016;42(9):1437-1444. doi:10.1007/s00134-016-4452-y
55. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: The prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5):847-856. doi:10.1007/s00134-012-2787-6
56. Fanelli V, Ranieri M V., Mancebo J, et al. Feasibility and safety of low-flow extracorporeal carbon dioxide removal to facilitate ultra-protective ventilation in patients with moderate acute respiratory distress syndrome. *Crit Care*. 2016;20(1):36. doi:10.1186/s13054-016-1211-y

57. Funakubo A, Taga I, McGillicuddy JW, Fukui Y, Hirschl RB, Bartlett RH. Flow vectorial analysis in an artificial implantable lung. *ASAIO J*. 2003;49(4).
58. Meyer AD, Rishmawi AR, Kamucheka R, et al. Effect of blood flow on platelets, leukocytes, and extracellular vesicles in thrombosis of simulated neonatal extracorporeal circulation. *J Thromb Haemost*. 2020;18(2):399-410. doi:10.1111/jth.14661
59. Okorie UM, Denney WS, Chatterjee MS, Neeves KB, Diamond SL. Determination of surface tissue factor thresholds that trigger coagulation at venous and arterial shear rates: Amplification of 100 fM circulating tissue factor requires flow. *Blood*. 2008;111(7). doi:10.1182/blood-2007-08-106229
60. Chan CHH, Ki KK, Zhang M, et al. Extracorporeal Membrane Oxygenation-Induced Hemolysis: An In Vitro Study to Appraise Causative Factors. *Membranes (Basel)*. 2021;11(5). doi:10.3390/MEMBRANES11050313
61. Makhro A, Huisjes R, Verhagen LP, et al. Red cell properties after different modes of blood transportation. *Front Physiol*. 2016;7(JUL). doi:10.3389/fphys.2016.00288
62. Sharma AS, Weerwind PW, Bekers O, Wouters EM, Maessen JG. Carbon dioxide dialysis in a swine model utilizing systemic and regional anticoagulation. *Intensive care Med Exp*. 2016;4(1):2. doi:10.1186/s40635-016-0076-3
63. Cardenas VJ, Miller L, Lynch JE, Anderson MJ, Zwischenberger JB. Percutaneous venovenous CO2 removal with regional anticoagulation in an ovine model. *ASAIO J*. 2006;52(4):467-470. doi:10.1097/01.mat.0000227743.07743.5d
64. Morimont P, Habran S, Desaive T, et al. Extracorporeal CO2 removal and regional citrate anticoagulation in an experimental model of hypercapnic acidosis. *Artif Organs*. 2019;43(8):719-727. doi:10.1111/aor.13431
65. Scaravilli V, Di Girolamo L, Scotti E, et al. Effects of sodium citrate, citric acid and lactic acid on human blood coagulation. *Perfus (United Kingdom)*. 2018;33(7). doi:10.1177/0267659118777441
66. Zheng Y, Xu Z, Zhu Q, et al. Citrate Pharmacokinetics in Critically Ill Patients with Acute Kidney Injury. *PLoS One*. 2013;8(6):1-7. doi:10.1371/journal.pone.0065992
67. Zanella A, Patroniti N, Isgrò S, et al. Blood acidification enhances carbon dioxide removal of membrane lung: An experimental study. *Intensive Care Med*. 2009;35(8):1484-1487. doi:10.1007/s00134-009-1513-5
68. Zanella A, Mangili P, Giani M, et al. Extracorporeal carbon dioxide removal through ventilation of acidified dialysate: An experimental study. *J Hear Lung Transplant*. 2014;33(5):536-541. doi:10.1016/j.healun.2013.12.006
69. Zanella A, Giani M, Redaelli S, et al. Infusion of 2.5 meq/min of lactic acid minimally increases CO2 production compared to an isocaloric glucose infusion in healthy anesthetized, mechanically ventilated pigs. *Crit Care*. 2013;17(6):R268. doi:10.1186/cc13098
70. Scaravilli V, Kreyer S, Belenkiy S, et al. Extracorporeal Carbon Dioxide Removal Enhanced by Lactic Acid Infusion in Spontaneously Breathing Conscious Sheep. *Anesthesiology*. 2016;124(3):674-682. doi:10.1097/ALN.0000000000000995
71. Bels D De, Pierrakos C, Spapen HD, Honore PM. A Double Catheter Approach for Extracorporeal CO2 Removal Integrated Within a Continuous Renal Replacement Circuit. *J Transl Intern Med*. 2018;6(4):157-158. doi:10.2478/JTIM-2018-0030
72. Moossavi S, Vachharajani TJ, Jordan J, Russell GB, Kaufman T, Moossavi S. Retrospective analysis of catheter recirculation in prevalent dialysis patients. *Semin Dial*. 2008;21(3):289-292. doi:10.1111/J.1525-139X.2008.00442.X
73. Schwärzel LS, Jungmann AM, Schmoll N, et al. Comparison of circular and parallel-plated membrane lungs for extracorporeal carbon dioxide elimination. *Membranes (Basel)*. 2021;11(6). doi:10.3390/membranes11060398
74. Allardet-Servent J, Castanier M, Signouret T, Soundaravelou R, Lepidi A, Seghboyan J-M. Safety and Efficacy of Combined Extracorporeal CO2 Removal and Renal Replacement Therapy in Patients With Acute Respiratory Distress Syndrome and Acute Kidney Injury. *Crit Care Med*. 2015;43(12):2570-2581. doi:10.1097/CCM.0000000000001296
75. Schmidt M, Jaber S, Zogheib E, Godet T, Capellier G, Combes A. Feasibility and safety of low-flow extracorporeal CO2 removal managed with a renal replacement platform to enhance lung-protective ventilation of patients with mild-to-moderate ARDS. *Crit Care*. 2018;22(1). doi:10.1186/S13054-018-2038-5
76. Nentwich J, Wichmann D, Kluge S, Lindau S, Mutlak H, John S. Low-flow CO2 removal in combination with renal replacement therapy effectively reduces ventilation requirements in hypercapnic patients: a pilot study. *Ann Intensive Care*. 2019;9(1):3. doi:10.1186/S13613-019-0480-4
77. Zanella A, Castagna L, Salerno D, et al. Respiratory electrodialysis a novel, highly efficient extracorporeal CO<inf>2</inf> removal technique. *Am J Respir Crit Care Med*. 2015;192(6):719-726. doi:10.1164/rccm.201502-0289OC
78. Jeffries RG, Lund L, Frankowski B, Federspiel WJ. An extracorporeal carbon dioxide removal (ECCO2R) device operating at hemodialysis blood flow rates. *Intensive Care Med Exp* . 2017;5(1):1-12. doi:10.1186/s40635-017-0154-1

79. Esposito R, Esposito I, Imperatore F, et al. Decapneization as supportive therapy for the treatment of status asthmaticus: a case report. *J Med Case Rep*. 2021;15(1):1-4. doi:10.1186/S13256-021-02689-6/FIGURES/4
80. Hospach I, Goldstein J, Harenski K, et al. In vitro characterization of PrismaLung+: a novel ECCO2R device. *Intensive Care Med Exp*. 2020;8(1). doi:10.1186/s40635-020-00301-7
81. CO2 Reset – Eurosets. https://www.eurosets.com/en/product/co2-reset/. Accessed November 25, 2024.
82. Huber W, Lorenz G, Heilmaier M, et al. Extracorporeal multiorgan support including CO2-removal with the ADVanced Organ Support (ADVOS) system for COVID-19: A case report. *Int J Artif Organs*. 2021;44(4):288-294. doi:10.1177/0391398820961781
83. Allescher J, Rasch S, Wiessner JR, et al. Extracorporeal carbon dioxide removal with the Advanced Organ Support system in critically ill COVID-19 patients. *Artif Organs*. 2021;45(12):1522. doi:10.1111/AOR.14044
84. Peek GJ, Killer HM, Reeves R, Sosnowski AW, Firmin RK. Early experience with a polymethyl pentene oxygenator for adult extracorporeal life support. *ASAIO J*. 2002;48(5):480-482. doi:10.1097/00002480-200209000-00007
85. Khoshbin E, Roberts N, Harvey C, et al. Poly-methyl pentene oxygenators have improved gas exchange capability and reduced transfusion requirements in adult extracorporeal membrane oxygenation. *ASAIO J*. 2005;51(3):281-287. doi:10.1097/01.MAT.0000159741.33681.F1
86. Toomasian JM, Schreiner RJ, Meyer DE, et al. A polymethylpentene fiber gas exchanger for long-term extracorporeal life support. *ASAIO J*. 2005;51(4):390-397. doi:10.1097/01.MAT.0000169111.66328.A8
87. Gaylor JDS. Membrane oxygenators: current developments in design and application. *J Biomed Eng*. 1988;10(6):541-547. doi:10.1016/0141-5425(88)90113-6
88. Roberts T., Wendorff D., Beely B., et al. Multi-day intensive care unit evaluation of a nitric oxide eluting extracorporeal life support circuit for heparin free ECCO2R. Supplement for the 10 th EuroELSO Congress 4–6 May 2022 London/UK. *Perfusion*. 2022;37(1_suppl):3-111. doi:10.1177/02676591221089240
89. Ontaneda A, Annich GM. Novel surfaces in extracorporeal membrane oxygenation circuits. *Front Med*. 2018;5(NOV):1-9. doi:10.3389/fmed.2018.00321
90. Kimmel JD, Arazawa DT, Ye SH, Shankarraman V, Wagner WR, Federspiel WJ. Carbonic anhydrase immobilized on hollow fiber membranes using glutaraldehyde activated chitosan for artificial lung applications. *J Mater Sci Mater Med*. 2013;24(11):2611-2621. doi:10.1007/s10856-013-5006-2
91. Arazawa DT, Kimmel JD, Finn MC, Federspiel WJ. Acidic sweep gas with carbonic anhydrase coated hollow fiber membranes synergistically accelerates CO2 removal from blood. *Acta Biomater*. 2015;25:143-149. doi:10.1016/j.actbio.2015.07.007
92. Straube TL, Farling S, Deshusses MA, Klitzman B, Cheifetz IM, Vesel TP. Intravascular Gas Exchange: Physiology, Literature Review, and Current Efforts. *Respir Care*. 2022;67(4):480. doi:10.4187/RESPCARE.09288
93. Douglas A, Jones N, Reed J. Calculation of whole blood CO2 content. *J Appl Physiol*. 1988;65(1):473-477.
94. Hodgkinson J, Tatam RP. Optical gas sensing: A review. *Meas Sci Technol*. 2013;24(1). doi:10.1088/0957-0233/24/1/012004
95. Barrett NA, Hart N, Camporota L. In vivo carbon dioxide clearance of a low-flow extracorporeal carbon dioxide removal circuit in patients with acute exacerbations of chronic obstructive pulmonary disease. *Perfus (United Kingdom)*. 2020;35(5):436-441. doi:10.1177/0267659119896531
96. Barrett NA, Hart N, Camporota L. In-vitro performance of a low flow extracorporeal carbon dioxide removal circuit. *Perfus (United Kingdom)*. 2020;35(3):227-235. doi:10.1177/0267659119865115
97. Cappadona F, Costa E, Mallia L, et al. Extracorporeal Carbon Dioxide Removal: From Pathophysiology to Clinical Applications; Focus on Combined Continuous Renal Replacement Therapy. *Biomedicines*. 2023;11(1):142. doi:10.3390/BIOMEDICINES11010142
98. Martins Costa A, Halfwerk F, Wiegmann B, Neidlin M, Arens J. Trends, Advantages and Disadvantages in Combined Extracorporeal Lung and Kidney Support From a Technical Point of View. *Front Med Technol*. 2022;4. doi:10.3389/FMEDT.2022.909990
99. Allescher J, Rasch S, Wiessner JR, et al. Extracorporeal carbon dioxide removal with the Advanced Organ Support system in critically ill COVID-19 patients. *Artif Organs*. 2021;45(12):1522-1532. doi:10.1111/aor.14044
100. Cove ME, MacLaren G, Federspiel WJ, Kellum JA. Bench to bedside review: Extracorporeal carbon dioxide removal, past present and future. *Crit Care*. 2012;16(5):232. doi:10.1186/cc11356
101. Taccone FS, Heiner MVM, Ferrari F, et al. Extracorporeal CO2 removal in critically ill patients: a systematic review. *Minerva Anestesiol*. 2017;83(7):762-772. doi:10.23736/S0375-9393.17.11835-3
102. Vivona L, Battistin M, Carlesso E, et al. Alkaline liquid ventilation of the membrane lung for extracorporeal carbon dioxide removal (Ecco2r): In vitro study. *Membranes (Basel)*. 2021;11(7):1-18. doi:10.3390/membranes11070464
103. Gonzalez FA, Santonocito C, Lamas T, et al. Is artificial intelligence prepared for the 24-h shifts in the ICU? *Anaesth Crit Care Pain Med*. 2024;43(6):101431. doi:10.1016/J.ACCPM.2024.101431

104. Zhang A, Haimowitz BJ, Tharwani K, Rojas-Peña A, Bartlett RH, Potkay JA. A Wearable Extracorporeal CO2 Removal System with a Closed-Loop Feedback. *Bioeng 2024, Vol 11, Page 969*. 2024;11(10):969. doi:10.3390/BIOENGINEERING11100969