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Review

Advancing extracorporeal carbon dioxide removal technology: bridging basic science and clinical practice

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Abstract

Recently, advancements in extracorporeal carbon dioxide removal ($ECCO_2R$) technology have markedly enhanced its clinical applicability and efficacy for managing severe respiratory conditions. This review highlights critical innovations in $ECCO_2R$, such as advanced catheter technologies, active mixing methods, and biochemical enhancements, which have substantially improved gas exchange efficiency and broadened the scope of $ECCO_2R$ applications. Integrating $ECCO_2R$ into acute and chronic respiratory care has led to a shift toward more mobile and less invasive modalities, promising for extending $ECCO_2R$ usage from intensive care units to home settings. By examining these technological advancements and their clinical impacts, this paper outlines the potential future directions of $ECCO_2R$ technology, emphasizing its role in transforming respiratory care practices and enhancing patient outcomes.

Key Words: active mixing; catheter design; $ECCO_2R$; gas exchange; integrated health systems; respiratory support; wearable technologies

Introduction

Extracorporeal carbon dioxide removal ($ECCO_2R$) is a specialized form of respiratory support designed primarily to remove carbon dioxide (CO_2) from the blood. This technology stems from initial observations made during renal replacement therapy with a hollow-fiber dialyzer, where significant CO_2 reduction was noted. Since then, $ECCO_2R$ technologies have been developed to address acute respiratory failure and acute respiratory distress syndrome (ARDS), providing vital alternatives when conventional ventilation is insufficient.[1] Historically, in 1972, Sherlock et al.[2] observed transient mild hypoxemia in patients treated with hemodialysis due to alveolar hypoventilation due to CO_2 removal by the hemofilter. These findings suggest the potential for respiratory control via artificial kidneys or lungs.[3] $ECCO_2R$ has been continuously developed and refined after these initial observations to improve patient outcomes in various critical care settings.

The clinical necessity for $ECCO_2R$ has become increasingly evident, especially in the management of treatment-resistant ARDS and severe coronavirus disease 2019 (COVID-19) patients. Recent advancements, such as the VENT-AVOID trial,[4] have demonstrated $ECCO_2R$'s ability to reduce the need for invasive ventilation during chronic obstructive pulmonary disease (COPD) exacerbations.

Studies have shown the efficacy of $ECCO_2R$ in improving gas exchange and reducing ventilator-induced lung injury (VILI) by enabling lower tidal volumes and decreased ventilator pressures.[1] During the COVID-19 pandemic, Cambria et al.[5] highlighted the role of $ECCO_2R$ in de-escalating ventilatory support, significantly impacting the management of high-risk patients. Thus, $ECCO_2R$ is crucial in managing severe respiratory disorders, offering a pathway to recovery or acting as a support mechanism during lung recovery. As technology advances, the application of $ECCO_2R$ continues to expand, driven by its potential to provide life-saving support in critical care environments. Recent guidelines from the European Society of Intensive Care Medicine recommend against the routine use of $ECCO_2R$ for treating ARDS not associated with COVID-19 outside of randomized controlled trials.[6] This recommendation is based on evidence indicating no mortality prevention benefit in such cases. For severe ARDS due to COVID-19, the recommendation against routine use remains strong, albeit on the basis of moderate evidence owing to indirectness.

Despite these recommendations, the potential benefits of $ECCO_2R$ in specific clinical scenarios should not be dismissed. $ECCO_2R$ can significantly aid in managing hypercapnia when conventional ventilation strategies risk inducing VILI, particularly in patients with severe lung compliance issues.[7] $ECCO_2R$ has shown a high success rate in patients with severe asthma.[7]

In these instances, $ECCO_2R$ enables ultraprotective lung ventilation by reducing tidal volumes and airway pressures, thereby minimizing VILI. Moreover, $ECCO_2R$ can act as a bridge to recovery or lung transplantation for patients with refractory hypercapnia, providing a lifesaving alternative when other treatments are inadequate.

Given the clinical benefits and complexities associated with ARDS, the application of $ECCO_2R$ should be considered within a comprehensive clinical assessment, preferably within the structured environment of clinical research, to further evaluate its efficacy and safety across different ARDS subtypes (**Table 1**).

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Table 1 | Clinical applications and recommendations for $ECCO_2R$ use

Clinical condition	$ECCO_2R$ application	Guidelines and evidence
ARDS	Limited to experimental use outside of controlled trials	Strong recommendation: Avoid routine use. High evidence
COVID-19 related ARDS	Employed in severe cases to mitigate ventilator-induced injuries	Moderate evidence: Use cautiously; avoid as routine treatment
Treatment-resistant hypercapnia	Enables ultraprotective lung ventilation to prevent further lung injury	Specific use: Advised for reducing VILI in severe lung compliance issues
Bridge to lung transplantation	Acts as a temporary support in refractory hypercapnia cases	Selective use: Based on individual patient assessment

ARDS: Acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; $ECCO_2R$: extracorporeal carbon dioxide removal; VILI: ventilator-induced lung injury.

This review aims to critically examine the evolution, current applications, and clinical efficacy of $ECCO_2R$ technologies. This includes a detailed analysis of how $ECCO_2R$ is used to manage acute respiratory failure, particularly in the context of ARDS and severe COVID-19 cases, despite varying recommendations. We aim to highlight the technological advancements that have facilitated its adoption and the ongoing clinical debates regarding its utility. By reviewing the latest evidence, this paper seeks to clarify the scenarios in which $ECCO_2R$ provides the greatest benefit and explore future research and clinical practice directions.

Methods for Literature Review

The literature review was conducted via Web of Science and PubMed to gather peer-reviewed articles. Keywords such as $ECCO_2R$, respiratory support, active mixing, wearable technologies, ARDS, COVID-19, and COPD were used, and Boolean operators were employed to refine the search results. The inclusion criteria focused on peer-reviewed studies published in English in the past 10 years, highlighting technological advancements, clinical applications, and physiological impacts of $ECCO_2R$. Exclusion criteria included the omission of non-peer-reviewed articles and studies unrelated to $ECCO_2R$. The selected studies were screened for relevance and quality, with data extracted on technological innovations, clinical outcomes, and physiological mechanisms. This systematic approach aimed to provide a comprehensive and unbiased overview of $ECCO_2R$ technology and its clinical implications.

Physiology of Blood Gas Transfer in the Lung and in the Membrane Lung

Oxygenation and CO_2 removal in the lung require fundamentally different physiological mechanisms, which are critical to understand when technologies such as $ECCO_2R$ are implemented. While the natural lung primarily utilizes the differential solubility and partial pressures of gases, $ECCO_2R$ systems can optimize these processes under controlled conditions.[4] A meta-analysis revealed that $ECCO_2R$ effectively reduces $PaCO_2$ and acidosis, facilitating less invasive ventilation strategies.[8]

Oxygenation dynamics

The oxygenation process in the lungs is limited by the relatively high saturation of venous blood (60–80%), which constrains the amount of oxygen (O_2) that can bind to hemoglobin. At normal venous oxygen tension and pH, no more than 40–60 mL of O_2 can be added per liter of venous blood. This physiological constraint necessitates a pulmonary blood flow of 4–6 L/min to meet an average oxygen consumption of approximately 250 mL/min. The equation governing this relationship highlights the dependency on hemoglobin concentration and oxygen saturation levels[9]:

$$\text{Oxygen content} = (Hb \times 1.34 \times SaO_2) + (0.0031 \times PaO_2) \qquad (1)$$

where Hb is the hemoglobin level, SaO_2 is the arterial oxyhaemoglobin saturation, and PaO_2 is the arterial partial pressure of oxygen. Under normobaric conditions, the maximum blood oxygen content is approximately 15 to 20 mL O_2/dL, which is constrained by the hemoglobin concentration.

CO_2 removal dynamics

In contrast, CO_2 is 20 times more soluble in plasma than is oxygen, facilitating its removal even at lower blood flows.[9] The venous blood CO_2 content is typically approximately 52 vol%, dropping to 48 vol% in arterial blood. This 4% reduction per circulation underlies the body's ability to expel CO_2 effectively. Approximately 90% of transported CO_2 is converted into bicarbonate, with the remainder either dissolved in plasma or bound to hemoglobin and proteins.[10] Given the greater solubility of CO_2, $ECCO_2R$ can efficiently remove CO_2 with significantly lower blood flow, provided that alveolar ventilation is adequately maintained. This dynamic is particularly advantageous in clinical settings where minimizing blood flow through the device reduces the risk of hemodynamic instability and blood trauma[11,12] (**Figure 1**).

Extracorporeal Carbon Dioxide Removal System Configurations and Components

Understanding the integration of $ECCO_2R$ systems with the physiological principles of gas exchange is crucial for optimizing their use in clinical scenarios (**Table 2**). These technologies enhance the natural capabilities of the lungs, adapting to patient-specific needs for CO_2 removal and oxygen delivery. The ability to customize blood flow and oxygenation levels through advanced pump technologies directly addresses the unique challenges of different patient conditions, such as those with severe lung compliance issues or those undergoing recovery from acute respiratory failure.[11] This technological synergy enhances the overall efficacy of $ECCO_2R$ in clinical settings, offering more precise control over gas exchange and reducing the burden on the natural lungs.

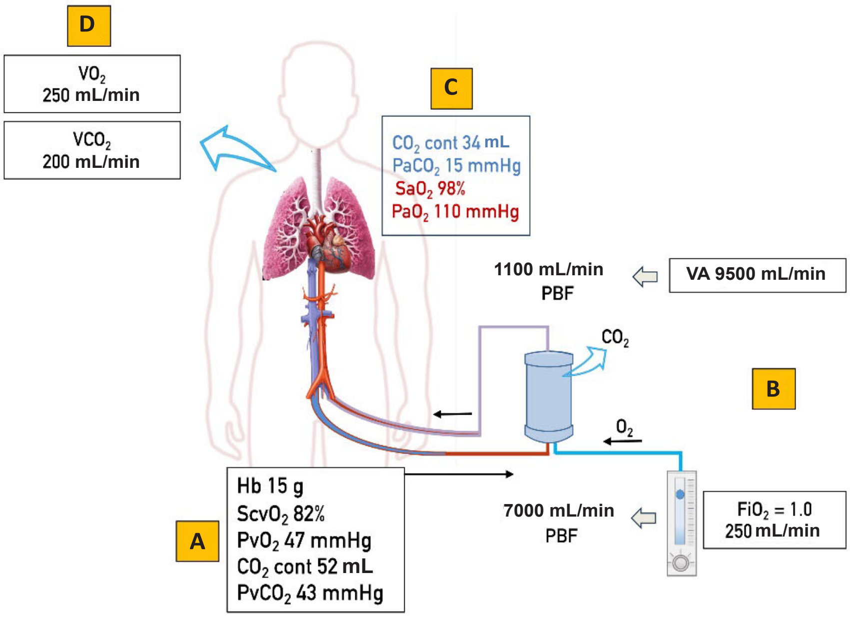

Figure 1 | Schematic diagram of the $ECCO_2R$ system and blood gas exchange.
This schematic diagram illustrates the $ECCO_2R$ circuit process, highlighting the blood flow through the system and the gas exchange that occurs. Initial blood parameters before entering the $ECCO_2R$ system are shown (A). The system's oxygen delivery setup is indicated (B), with postexchange blood parameters detailed after CO_2 removal and O_2 enrichment (C). Overall gas exchange rates, including oxygen consumption and CO_2 production, are summarized (D). The diagram visually represents the efficiency of $ECCO_2R$ in managing blood gas levels. Created with Microsoft PowerPoint for Mac Version 16.86 (24060916). CO_2: Carbon dioxide; cont: content; $ECCO_2R$: extracorporeal carbon dioxide removal; FiO_2: fraction of inspired O_2; Hb: hemoglobin; O_2: dioxygen; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen; PBF: pump blood flow; $PvCO_2$: partial pressure of carbon dioxide in venous blood; PvO_2: partial pressure of oxygen in venous blood; SaO_2: arterial oxygen saturation; $sCVO_2$: central venous oxygen saturation; VA: venoarterial; VCO_2: carbon dioxide output; VO_2: oxygen uptake.

Table 2 | Key components of $ECCO_2R$ systems

Component	Description	Examples
Blood pump	Facilitate the movement of blood through the system; can be mechanical or use natural pressure	Displacement pumps, rotary pumps
Membrane lung	The site of gas exchange, specifically optimized for CO_2 removal rather than oxygenation	Poly(4-methyl-1-pentene) membranes
Access cannula	Provide the connection between the patient's bloodstream and the $ECCO_2R$ system	Arterial and venous cannulas
Control systems	Monitor and adjust the operation parameters such as blood flow, pressure, and gas exchange rate	ProLUNG Meter, infrared sensors

CO_2: Carbon dioxide; $ECCO_2R$: extracorporeal carbon dioxide removal.

Extracorporeal carbon dioxide removal configurations

$ECCO_2R$ systems can be broadly categorized into two configurations on the basis of the type of vascular access used: arteriovenous ($AVCO_2R$) and venovenous ($VVCO_2R$). Each configuration is designed to meet specific clinical needs and comprises three main components: a blood pump, a membrane lung, and an access cannula, which can be customized by combining optimal components according to the patient's condition and the capabilities of the medical center.

Blood pump for extracorporeal carbon dioxide removal

In extracorporeal life support (ECLS) devices, blood pumps are crucial in substituting wholly or partially for the heart's functionality to generate blood flow. Blood pumps are generally divided into two categories: displacement pumps and rotary pumps. Displacement pumps, such as roller (or peristaltic) pumps, operate through periodic changes in the working space volume. Moreover, rotary pumps, such as centrifugal pumps, transfer energy to the fluid through velocity changes induced by the impeller vanes. The two primary types of blood pumps used in ECLS applications are roller (or peristaltic) pumps and centrifugal pumps, as shown in **Figure 2**. Each type has specific operational characteristics and applications depending on the requirements of the ECLS procedure.[13]

Peristaltic pumps

Also known as roller pumps, these devices use a length of polyvinyl chloride or silicone tubing compressed cyclically by rollers. The rollers push against curved metal backing, allowing controlled movement of blood through the tube. This type of pump is known for delivering a consistent blood volume independent of the outlet load.[14] This characteristic makes roller pumps particularly useful in applications where precise control of blood flow is necessary, such as cardiopulmonary bypass during surgical procedures. They are also beneficial because they prevent backflow and allow the flow direction to be easily reversed.[14] However, the shear stress caused by the rollers can damage blood cells, leading to complications such as hemolysis. Early extracorporeal systems often utilized peristaltic pumps as positive displacement pumps. This method, while cost-effective and reliable, historically posed risks of blood trauma, such as hemolysis, especially at relatively high flow rates.[15] Modern peristaltic pumps have been significantly refined to reduce these risks, particularly in settings such as hemodialysis, where lower flow rates are prevalent.[16]

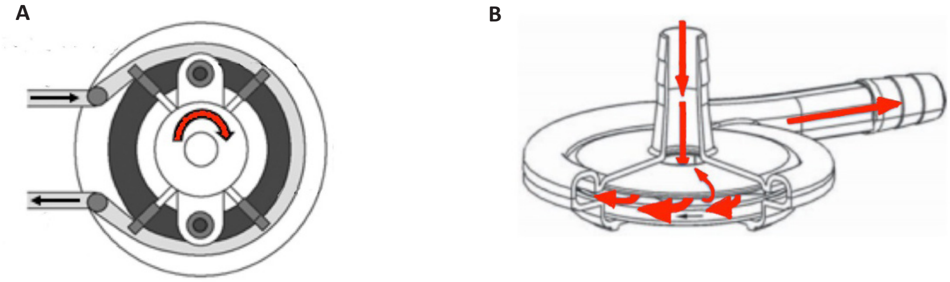

Figure 2 | **Peristaltic and centrifugal pumps.**

The image presents two different types of pumps used for fluid movement. (A) A side view of a peristaltic pump. The diagram illustrates how the flexible tubing is sequentially compressed by rotating elements (rollers), which propel the fluid through the tube. The red arrows indicate the movement of fluid caused by the compression of the tube. This type of pump is ideal for maintaining fluid sterility and preventing contamination, as the fluid never comes into direct contact with the pump's moving mechanical parts. (B) A top view of a centrifugal pump. The design shows a central rotating body (indicated by the curved red arrow), which creates a movement of fluid from the center outward. The black arrows indicate the fluid inlet and outlet ports. This mechanism relies on centrifugal forces to move the fluid (refer to **Figure 3**). Created with Adobe Illustrator (version 25.2.3).

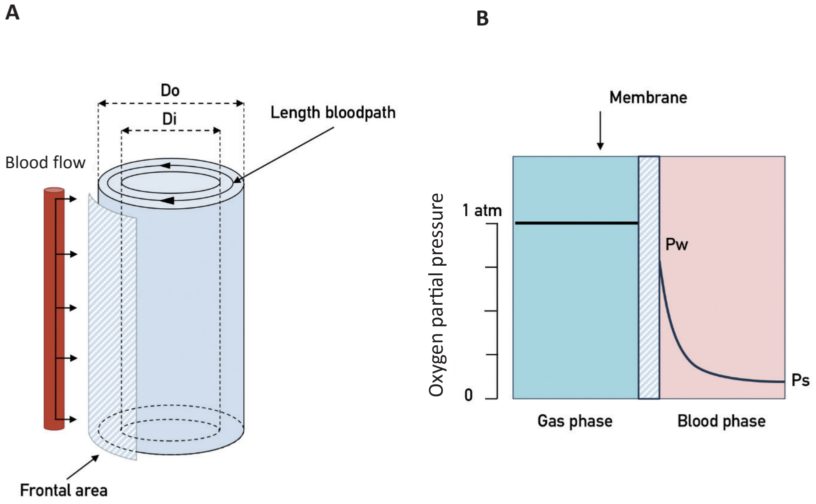

Figure 3 | **Design and gas exchange dynamics of the membrane lung in the $ECCO_2R$ system.**

This figure illustrates the design and functionality of a membrane lung used in $ECCO_2R$ systems. (A) How blood flows through the cylindrical membrane, optimizing the surface area for gas exchange. (B) The oxygen partial pressure gradient across the membrane, which is essential for efficient gas exchange. Created with Microsoft PowerPoint for Mac Version 16.86 (24060916). atm: Atmospheric pressure; Di: inner diameter; Do: outer diameter; $ECCO_2R$: extracorporeal carbon dioxide removal; Ps: partial pressure in the solution/blood; Pw: partial pressure in the water phase.

Centrifugal pumps

These pumps create blood flow through a vortex effect within a pumping chamber where a rotating impeller generates a low-pressure zone at the center and a high-pressure zone at the periphery. The blood flow in centrifugal pumps depends on the revolutions per minute of the impeller and the pressure differential across the pump, making them sensitive to changes in downstream resistance. This sensitivity necessitates direct measurement of blood flow to ensure proper perfusion. Advancements in centrifugal pump technology, including magnetic levitation, have significantly reduced the risk of hemolysis and thrombus formation, making these pumps preferable for long-term support in extracorporeal systems. Rotary pumps, especially centrifugal pumps, are designed to operate in regions of lower cell destruction, balancing shear stress and transition time to minimize hemolysis and platelet activation.[17]

Newer models employ magnetic levitation or hydrodynamic bearings to allow the impeller, eliminating mechanical contact and significantly reducing friction, heat generation, and thrombus formation.[18,19] This technology offers substantial advantages regarding hemolysis reduction, thrombogenesis minimization, and mechanical durability, which are essential for long-term mechanical circulatory support.

For $AVCO_2R$, the natural arteriovenous pressure gradient can be utilized as an alternative to mechanical pumps. The extracorporeal blood flow generated by this gradient can achieve rates between 1 and 2.5 L/min, sufficient for effective CO_2 removal if the mean arterial pressure is maintained at 70 mmHg and the cardiac index is above 3 L/min/m².[11] Conversely, $VVCO_2R$ requires a mechanical blood pump to ensure adequate blood flow.[11]

Membrane lungs in extracorporeal carbon dioxide removal systems

A membrane lung, more aptly referred to as a membrane oxygenator in the context of $ECCO_2R$, is utilized primarily for CO_2 removal rather than oxygenation. This distinction is important because $ECCO_2R$ systems are often optimized for CO_2 extraction efficiency, which differs fundamentally from oxygen delivery mechanisms.

Design and functionality

Membrane oxygenators are sophisticated devices essential for providing respiratory and circulatory support.[20] They use advanced designs to optimize the gas exchange between blood and air. These systems include several critical components, such as blood ports, air filters, gas ports, and bundles of hollow fibers, each of which is vital for efficient operation.[12]

There are two primary types of membrane oxygenators, each designed with specific features to suit different clinical needs. The first type has a large frontal area and a short path for blood to travel through the membrane. This design maximizes the gas exchange rate because the greater membrane surface is exposed to the blood. Additionally, the short path reduces resistance to blood flow, resulting in a low-pressure drop. This configuration is particularly beneficial in scenarios requiring rapid oxygenation of large blood volumes, such as during acute respiratory distress or major surgical procedures.[21,22]

The second type features a smaller frontal area with a longer blood path. This setup increases the contact time between the blood and the membrane, potentially enhancing the gas exchange efficiency despite the greater pressure drop. The reduced membrane area can be advantageous when space and resource efficiency are paramount. This design is particularly useful in situations where the benefits of a smaller device outweigh the drawbacks of increased pressure drops, such as in neonatal care or for patients with limited vascular access.[22]

In terms of design improvements, these oxygenators often utilize extraluminal flow, where blood flows around rather than inside the hollow fibers, such as in hemodialyzers. This method creates a more tortuous path for the blood, enhancing gas transfer efficiency by increasing contact with the gas exchange surfaces. The fibers can be organized in various structural configurations to further optimize performance.[23] For example, arranging the fibers in a woven mat can improve secondary mixing and reduce the likelihood of blood shunting. Alternatively, spiraling the fibers around a central core with precisely controlled spacing and angles can maximize blood exposure to the gas exchange surface, enhancing efficiency and minimizing the device's priming volume.[23]

These advancements in membrane oxygenator technology represent a significant evolution from earlier oxygenation methods. They offer critical support in various clinical settings and enhance patient outcomes by efficiently oxygenating blood while minimizing potential complications.

Operational requirements

For effective operation in $ECCO_2R$ applications, the membrane lung must meet several criteria:

- Minimal priming volume to reduce hemodilution risk.
- A sufficient surface area ensures effective gas exchange.
- High biocompatibility minimizes inflammatory reactions.
- Durability and ease of replacement in case of failure.

Compared with extracorporeal membrane oxygenation systems, $ECCO_2R$ systems generally feature smaller membrane surfaces (0.33–1.3 m²) (≥ 1.8 m²). This size difference is suitable because $ECCO_2R$ can achieve efficient CO_2 removal at lower blood flow rates by increasing the sweep gas flow.

Gas transfer dynamics

Gas transfer within the membrane lung operates on the principle of diffusion. The diffusion flux of gases (J) depends on the partial pressure gradient between the blood and gas phases (δP), the diffusive characteristics of the gas (D), and the membrane thickness (δx). An increase in the gas transfer rate can be achieved by increasing the partial pressure difference, enlarging the diffusion surface area, or reducing the diffusion distance. Practical limitations exist, such as potential increases in the device's priming volume or the pressure drop across the membrane if these parameters are adjusted too far.

Additionally, CO_2 removal exhibits biphasic kinetics, starting with a rapid decline due to the initial extraction of dissolved CO_2, followed by a steadier phase as CO_2 is released from bicarbonate.[24] Modern materials such as no microporous poly(4-methyl-1-pentene) have been introduced to improve gas exchange and biocompatibility while reducing susceptibility to plasma leakage.[25] Moreover, enhancing membrane surfaces with covalently bound heparin can reduce thrombogenicity, further optimizing the performance of membrane lungs in clinical settings.[26]

Vascular access in extracorporeal carbon dioxide removal systems

Vascular access selection is crucial for effective $ECCO_2R$ and is determined by the specific system configuration—$AVCO_2R$ or $VVCO_2R$. $AVCO_2R$ typically employs single-lumen catheters for arterial and venous access, usually ranging from 13–15 French for arterial access and 15–21 French for venous access.[27,28] In contrast, $VVCO_2R$ systems often utilize double-lumen cannulas inserted percutaneously in femoral–femoral or femoral–jugular configurations to optimize hemodynamics and enhance procedural safety.[26,27]

Recent advancements have introduced heparin-coated, wire-reinforced cannulas that enhance biocompatibility and reduce thrombogenic complications. Notably, high-flow, wire-reinforced double-lumen catheters, especially those inserted via the right internal jugular vein, play a pivotal role in reducing recirculation and improving the efficiency of CO_2 removal.[29]

Impact of catheter geometry on system performance

The geometry and diameter of the catheter significantly influence hydraulic resistance and overall system efficiency. Coaxial catheters, known for their larger diameter, have been shown to offer superior flow profiles, minimizing shear stress and optimizing gas exchange. These are essential for maintaining effective blood flow while reducing pressure drops across the system.[30] The relationship between catheter size and hydraulic resistance is well explained by Hagen–Poiseuille's law, which states that the flow rate is proportional to the fourth power of the catheter's diameter.

Comparative studies of catheter cross-sectional geometries—circular, semicircular, and coaxial—have demonstrated that coaxial catheters, despite their larger diameter, are more efficient in managing hydraulic resistance. These studies have also shown that the side hole size significantly affects the pressure drop, with smaller holes causing substantial pressure drops due to severe flow distortions at the lumen entrance.[27,28]

Recent developments include high-flow, wire-reinforced double-lumen catheters placed via the right internal jugular vein, where the drainage port is advanced into the intrahepatic inferior vena cava under ultrasound guidance, aligning the return port with the right atrium to minimize recirculation.[31] Additionally, arterial chimney graft cannulation has been developed as a new technique for $ECCO_2R$, which is particularly beneficial for patients with small arterial vessels or a history of heart–lung transplantation, providing alternative access that accommodates anatomical limitations.[32] These technological and procedural advancements in vascular access for $ECCO_2R$ are critical for enhancing treatment efficacy and safety, broadening its clinical applications, and improving patient outcomes.

Significance and Development of CO_2 Sensors

The role of CO_2 sensors in ECLS systems is crucial for ensuring effective patient monitoring and management. These sensors are integral in measuring the concentration of CO_2 in the blood, which is a critical parameter for assessing a patient's respiratory function. Historically, CO_2 measurement has been a vital component of emergency, intensive care, and anesthesia, providing noninvasive insights into pulmonary function.

Recent advancements in sensor technology have driven significant improvements in ECLS applications, particularly in $ECCO_2R$ and extracorporeal membrane oxygenation. These advancements address the need for precise, real-time monitoring in critical care settings. Traditional sensors often face challenges such as condensation and temperature variability, which could compromise their accuracy and reliability.[33]

The development of the novel optical CO_2 sensor presented in this research represents a significant improvement in overcoming these challenges. This sensor is designed with an advanced optical system that prevents condensation, a common issue in the humid environments of ECLS systems.[33] It employs nondispersive infrared technology to achieve high precision in CO_2 measurement, ensuring stable performance even under varying physiological conditions. The sensor architecture includes a heating mechanism that maintains a consistent operating temperature, further enhancing its reliability.[33-35]

In vitro and *in vivo* validation tests have demonstrated the superior performance of the sensor compared with existing technologies. It showed exceptional accuracy, with measurement deviations within ±2% of the reference values, and maintained stability across different test scenarios.[33] These results underscore the sensor's potential to significantly improve patient outcomes by providing more accurate and reliable CO_2 monitoring.[33] By integrating this innovative sensor into ECLS systems, healthcare providers can achieve better control over patient treatment, reducing the risks associated with traditional sensor limitations. This advancement enhances the efficacy of ECLS procedures and opens new avenues for research and development in respiratory care technologies. This novel CO_2 sensor represents a critical step toward more effective and reliable ECLS systems, ultimately improving patient care and safety in critical medical environments.

Monitoring parameters in extracorporeal carbon dioxide removal during treatment

During $ECCO_2R$, monitoring the status of the system and treatment efficiency is important. Blood flow through the integrated lung assist (iLA) is measured via a clamp-on transducer (transit time ultrasound flowmeter) during $AVCO_2R$ with high precision (NovaFlow®, Novalung, Hechingen, Germany).[36] The peristaltic pumps estimate the flow rate on the basis of the tube inner diameter, pump head size and pump head revolutions per minute for $VVCO_2R$, and they achieve high accuracy for flow rates < 500 mL/min.[16] Some $ECCO_2R$ devices are equipped with bubble detectors and clamps to prevent embolism.[37] Sweep gas flow is also monitored by an infrared sensor.[38] Blood temperature in the extracorporeal circuit can also be monitored when $ECCO_2R$ is combined with renal replacement therapy devices equipped with a fluid warmer/heater.[39] The hydrostatic pressure at the inlet/outlet of the membrane lung is monitored by pressure transducers.[40] Recently, it has also been used to monitor CO_2 concentrations during $ECCO_2R$ (Prolung®, Estor, Italy). The device Prolung Meter supplies medical-grade air to the cartridge for CO_2 removal; it monitors CO_2 removal with an optical nondispersive infrared sensor at the gas outlet during extracorporeal blood hemoperfusion.[41] The Prolung Meter controls the flow and air temperature and automatically increases the air flow to keep the lumen of the cartridge dry for CO_2 removal.[41]

Overview of commercial extracorporeal carbon dioxide removal devices and systems

$ECCO_2R$ devices are classified on the basis of their vascular access configuration, with the disease's stage and severity guiding the choice of technique. This classification influences the application's complexity and the potential for complications.[42] $AVCO_2R$ systems such as the Novalung system use a high blood flow rate (1–2.5 L/min) to facilitate CO_2 removal and oxygenation. This system operates either with a pump or as a pumpless unit, utilizing the patient's arteriovenous pressure gradient to drive blood through a membrane lung with a low-resistance design. Novalung features a poly(4-methyl-1-pentene) membrane that efficiently exchanges gases while minimizing pressure drop, which is suitable for patients with ARDS and severe asthma and as a bridge to lung transplantation.[43-49] $VVCO_2R$ systems are designed primarily for CO_2 removal at lower blood flow rates (300–500 mL/min). Systems such as DECAPsmart (Medica, Medolla, Italy) and iLA Active® (Xenios AG, Heilbronn, Germany) utilize various membrane lung and pump configurations to optimize CO_2 removal efficiency. DECAPsmart combines a neonatal polypropylene membrane lung with a polysulfone hemofilter to increase CO_2 elimination and reduce anticoagulation needs. On the other hand, iLA Activve® employs a magnetically suspended pump to manage different blood flow rates, minimizing hemolysis and enhancing CO_2 removal efficiency.[48,50] Recent innovations include the Hemolung RAS, which integrates a centrifugal pump with a membrane lung into a single unit, increasing the efficiency of CO_2 removal at lower flow rates.

Similarly, the PALP system (Pump Assisted Lung Protection', Maquet, Germany) represents a minimized extracorporeal membrane oxygenation setup designed for easier handling and integration in clinical settings. This system uses a large frontal area and short blood path in the membrane lung to optimize gas exchange, especially in emergency and intensive care scenarios.[22,51] Recent comparative studies have shown that certain membrane lungs, such as the Medos Hilite 800LT®, demonstrate superior CO_2 removal capabilities to others, such as the Maquet Quadrox-iD®, highlighting the importance of selecting the right component on the basis of specific clinical needs.[52] Integrating $ECCO_2R$ with renal replacement therapy opens new avenues for treating patients with combined pulmonary and renal failure. Systems such as DECAPsmart have shown the feasibility of such integrated approaches, potentially extending the scope of multiorgan support therapies to a broader range of clinical situations.[52-54] The choice of $ECCO_2R$ technology must be aligned with specific clinical requirements, including the severity of the patient's condition and the intended duration of use. As advancements continue, integrating these systems into clinical practice offers promising prospects for managing complex respiratory conditions.

Evidence and practical applications of extracorporeal carbon dioxide removal

In 2016, Fanelli et al.[55] reported that $ECCO_2R$ significantly reduced driving pressure during the first two days in ARDS patients. In 2020, Grasselli et al.[56] showed that $ECCO_2R$ effectively reduced arterial partial pressure of carbon dioxide, increased pH, and decreased the respiratory rate. In the same year, Combes et al.[57] discusses a consensus from a European round table meeting on the use of $ECCO_2R$ in intensive care unit settings for ARDS and severe acute exacerbations of COPD. The experts agreed that ARDS was the primary indication for $ECCO_2R$, with goals focusing on ultra-protective lung ventilation and managing CO_2 levels. In acute exacerbations of COPD, the criteria for $ECCO_2R$ initiation include risks of noninvasive ventilation failure and maintaining hemodynamic stability. The group recommended anticoagulation with intravenous heparin and highlighted the need for more research. In 2022, the REST trial assessed the impact of $ECCO_2R$ on 90-day mortality in patients with acute hypoxemic respiratory failure and reported no significant improvements.[58] In the same year, Consales et al.[59] demonstrated that $ECCO_2R$ combined with CRRT in ARDS and COPD patients effectively maintained CO_2 clearance and corrected pH, preventing noninvasive ventilation failure in 80% of patients without complications. In 2024, Cambria et al.[5] highlighted the critical role of $ECCO_2R$ in managing COVID-19-related ARDS, reducing the need for ventilatory support. Finally, a VENT-AVOID trial showed that $ECCO_2R$ can reduce the need for invasive ventilation during COPD exacerbations.[4]

$ECCO_2R$ has been increasingly recognized for its potential to manage severe respiratory distress syndromes, particularly in settings where traditional mechanical ventilation fails to suffice.[11] For example, during the COVID-19 pandemic, $ECCO_2R$ was a pivotal treatment strategy in several critical cases. Studies have highlighted the critical role of $ECCO_2R$ in de-escalating ventilatory support during severe ARDS challenges, including those related to COVID-19.[8] One notable case involved a 44-year-old patient suffering from COVID-19-associated ARDS, where $ECCO_2R$ allowed for a significant reduction in ventilator settings, thus minimizing VILI while facilitating adequate gas exchange.[60] This case, among others documented across various healthcare settings, exemplifies the adaptability of $ECCO_2R$ in critical care. The clinical applications and recent advancements in $ECCO_2R$ have been summarized through key prospective and retrospective studies and trials from the past 5 years (2019–2024). This comparison, highlighted in **Table 3**,[4,7,56,58,59,61-69] shows the evolution and current understanding of $ECCO_2R$ technology.

Despite its potential, the widespread adoption of $ECCO_2R$ faces several significant barriers. The technology and associated disposables can be prohibitively expensive, limiting its use to well-funded hospitals in developed countries.[70] Additionally, the operation of $ECCO_2R$ systems requires specialized training, which not all medical staff may have access to, necessitating extensive training programs.[71] Infrastructural changes in hospitals, such as the integration of specialized plumbing and power requirements for $ECCO_2R$ machines, pose logistical and financial challenges.[72] The versatility of $ECCO_2R$ could be expanded beyond the confinement of intensive care units. In low-resource settings, simplified versions of the technology could be developed to offer basic respiratory support, thus broadening the scope of $ECCO_2R$ applications to regions with limited access to advanced medical care. Moreover, there is potential for $ECCO_2R$ systems to be adapted for outpatient care, providing continuous support for patients with chronic respiratory conditions. This adaptation could help reduce hospital readmissions and support patients in their recovery phase at home, significantly enhancing their quality of life and reducing the burden on hospital resources.

Emerging Technologies and Future Directions in Extracorporeal Carbon Dioxide Removal

The realm of $ECCO_2R$ continues to evolve, with new technologies enhancing its efficacy and expanding its applicability. Building on the legacy of IVOX (intravascular oxygenator), recent developments have focused on optimizing gas exchange within $ECCO_2R$ catheters.[73] The Hattler catheter introduces active mixing via a rigid fiber mat around a central balloon, pulsating to direct blood flow over membrane fibers and enhance CO_2 exchange efficiency (**Figure 4**). This design minimizes fiber drag on blood flow, with animal trials showing that CO_2 exchange rates nearly double those of IVOX under similar conditions. Another approach involves rotating the fiber bundle in the dynamic intravascular lung assist device, which, despite the risk of damaging vessel walls, has shown promising CO_2 exchange rates.[74,75] These innovations indicate a shift toward more efficient and less invasive $ECCO_2R$ solutions.

Table 3 | Summary of clinical applications and new findings of ECCO2R (2019–2024)

Study	Year	Participants	Study type	Clinical application	Main outcome	Main findings
Duggal et al.[4] (VENT-AVOID trial)	2024	200	Randomized controlled trial	COPD exacerbations	Decreased invasive ventilation requirements	ECCO$_2$R can reduce the need for invasive ventilation during COPD exacerbations
Hu et al.[61]	2024	60	Randomized controlled trial	ECCO$_2$R combined with CRRT in ARDS	Diaphragmatic function and respiratory efficiency	ECCO$_2$R + CRRT significantly improved PaCO$_2$, MEP, MIP, diaphragm thickness, and activity compared to CRRT alone. Reduced oxidative stress and improved respiratory parameters
Pasero et al.[62]	2024	14	Case control study	ECCO$_2$R and CRRT in ARDS (COVID-19 and non-COVID-19)	Driving pressure, mortality	ECCO$_2$R + CRRT reduced driving pressure more effectively in COVID-19 ARDS patients, did not affect 28-d mortality, but reduced ventilation duration and intensive care unit stay
Alessandri et al.[63]	2023	150	Retrospective Mulicentric study	ECCO$_2$R with RRT in COVID-19 ARDS	Ventilator settings, renal function	ECCO$_2$R + RRT reduced tidal volume, driving pressure, and plasma creatinine. pH and PaCO$_2$ levels remained stable. No patient-related events reported
Tiruvoipati et al.[64]	2023	10	Observational study	ECCO$_2$R with PrismaLung+ in hypercapnic respiratory failure	pH, PaCO$_2$ levels, safety	PrismaLung+ improved pH and PaCO$_2$ levels rapidly, with no patient-related complications
Chiumello et al.[65]	2022	10	Prospective observational study	Ultraprotective ventilation with low-flow ECCO$_2$R	Mechanical power, gas exchange	Low-flow ECCO$_2$R reduced respiratory rate and mechanical power without compromising gas exchange, maintaining oxygenation
Consales et al.[59]	2022	17	Retrospective observational study	ECCO$_2$R combined with CRRT in ARDS and aeCOPD	Ventilation shift, extubation	ECCO$_2$R-CRRT effectively maintained CO$_2$ clearance and corrected pH, preventing NIV failure in 80% of patients without complications
McNamee et al.[58] (REST trial)	2022	411	Randomized controlled trial	Acute hypoxemic respiratory failure (REST)	No significant improvement in 90-d mortality	ECCO$_2$R's impact on long-term outcomes, showing no significant improvement in 90-d mortality
İnal and Efe[7]	2021	75	Retrospective study	Severe hypercapnic respiratory failure	Improved outcomes in severe hypercapnic respiratory failure	A high success rate of ECCO$_2$R in improving outcomes in patients with severe hypercapnic respiratory failure
Azzi et al.[66]	2021	60	Retrospective study	COPD exacerbation unresponsive to NIV	Managed acute exacerbations of COPD unresponsive to NIV	Demonstrated ECCO$_2$R's role in acute exacerbations of COPD unresponsive to NIV
Grasselli et al.[56]	2020	11	Retrospective study	Extracorporeal CO$_2$ removal in ARDS and chronic respiratory failure	Reduction in arterial PCO$_2$ and respiratory rate	ECCO$_2$R reduced PCO$_2$, increased pH, decreased respiratory rate
Augy et al.[67]	2019	70	Prospective study	Acute respiratory failure management	Utilization rate, efficacy, and safety	Low utilization rate, efficacy confirmed in COPD and ARDS, safety concerns (hemolysis, bleeding, thrombosis), and differences in device profiles
Richard et al.[68]	2019	35	Nonexperimental before-and-after multicenter study	Ultralow tidal volume ventilation in ARDS	Driving pressure, acidosis	Ultralow tidal volume (4 mL/kg) reduced driving pressure, caused transient severe acidosis in 32% of patients, and had a 41% mortality rate before day 90
Combes et al.[69] (SUPERNOVA study)	2019	95	Prospective study	Moderate ARDS	Proportion of patients achieving ultra-protective ventilation without significant increases in PaCO$_2$ and maintaining arterial pH > 7.30	ECCO$_2$R facilitate ultra-protective ventilation in patients with moderate ARDS

aeCOPD: Acute exacerbation of chronic obstructive pulmonary disease; ARDS: acute respiratory distress syndrome; CO$_2$: carbon dioxide; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; ECCO$_2$R: extracorporeal carbon dioxide removal; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; NIV: noninvasive ventilation; PaCO$_2$: partial pressure of carbon dioxide in arterial blood; REST: respiratory extracorporeal support trial; RRT: renal replacement therapy; VILI: ventilator-induced lung injury.

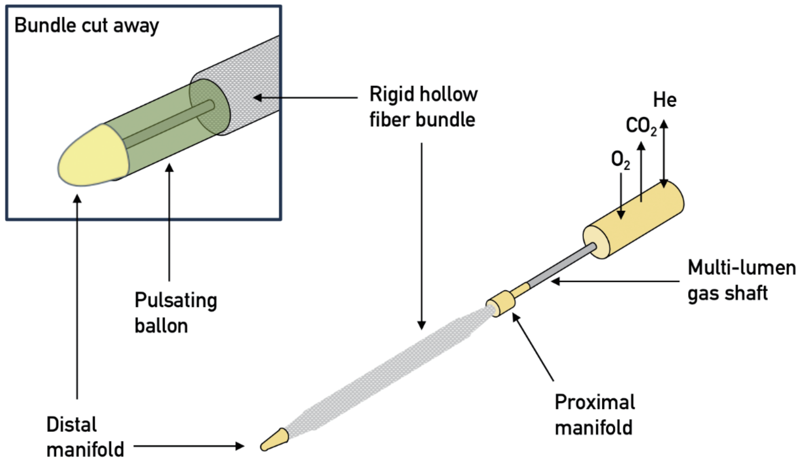

Figure 4 | Advanced ECCO2R catheter with an active mixing mechanism

This illustrates an advanced $ECCO_2R$ catheter design featuring a pulsating balloon within a rigid hollow fiber bundle. The multilumen gas shaft manages the input and output of gases, optimizing the gas exchange process. The distal and proximal manifolds ensure efficient blood flow through the catheter, enhancing the overall performance of $ECCO_2R$ therapy. Created with Microsoft PowerPoint for Mac Version 16.86 (24060916). CO_2: Carbon dioxide; $ECCO_2R$: extracorporeal carbon dioxide removal; He: helium; O_2: oxygen.

The covalent immobilization of carbonic anhydrase on the surface of hollow fiber membranes represents a significant advancement. This modification accelerates the conversion of bicarbonate to CO_2, facilitating faster gas removal and improving overall system efficiency. Such biochemical enhancements are crucial for developing more effective $ECCO_2R$ systems.[11]

Cressoni et al.[76] proposed an intriguing method involving the ultrafiltration of sodium bicarbonate and its replacement with a sodium hydroxide solution to increase the CO_2 removal efficiency. Similarly, preliminary studies have shown the potential of loading blood with metabolizable acids such as lactic acid to increase CO_2 tension and enhance passive transfer across membrane lungs.[74,76,77]

RAND has developed an innovative integrated device that combines cardiocirculatory assist functions with a membrane oxygenator capable of controlling blood temperature . Designed for ease of use by nonspecialized personnel, this compact, portable system can be deployed rapidly in various medical settings, including emergency and transport scenarios, highlighting the potential for mobile health applications.[78] The development of wearable $ECCO_2R$ technologies for chronic respiratory conditions, such as obstructive bronchitis or pneumonia, has significantly advanced. These devices provide continuous CO_2 removal, potentially transforming the management of chronic respiratory diseases by enhancing patient mobility and quality of life.

Patient impact

The implementation of $ECCO_2R$ significantly impacts patient outcomes and quality of life, particularly in severe respiratory conditions.[8] By reducing the need for invasive mechanical ventilation, $ECCO_2R$ can decrease the incidence of ventilator-associated complications such as VILI and barotrauma.[79] This gentle approach to managing CO_2 levels can lead to improved survival rates and faster recovery times for patients suffering from conditions such as ARDS[66] or severe COPD exacerbations.[7,51] Moreover, the ability of $ECCO_2R$ to maintain more stable CO_2 and oxygen levels contributes to less physiological stress in patients, which is critical in delicate respiratory conditions.[22,80] This stability often results in better overall patient comfort and less need for sedation, which are important factors in enhancing the quality of life during intensive care treatment.[80] As $ECCO_2R$ technology continues to evolve, it also opens the possibility for use in less acute settings, allowing for earlier discharge from the intensive care unit and even application in a homecare setting for chronic conditions, thus transforming long-term management strategies for chronic respiratory disease patients.[11,80]

Limitations

The present narrative review has several limitations. First, the heterogeneity of the included studies, with varying designs, patient populations, and outcomes, complicates the ability to draw uniform conclusions. Second, there is a potential for publication bias, as studies with positive outcomes are more likely to be published and included in the review. Third, the review may lack long-term follow-up data on the efficacy and safety of $ECCO_2R$, limiting the understanding of sustained impacts. Fourth, the quality of evidence varies, with some studies relying on observational data rather than randomized controlled trials, impacting the overall strength of the findings. Fifth, differences in $ECCO_2R$ technology and protocols across studies complicate comparisons and generalizations. Finally, the focus on conditions such as ARDS and COVID-19 may not fully capture the potential applications of $ECCO_2R$ in other respiratory or metabolic disorders.

Conclusion

This review highlights the significant advancements in the field of $ECCO_2R$, emphasizing its evolving role from an emergency intervention to a more routinely considered treatment in respiratory care. Innovations in $ECCO_2R$ technology have enhanced its efficacy and safety and broadened its potential applications, making it a critical component in managing complex respiratory disorders. Continued research and trials are essential to fully understand and optimize $ECCO_2R$ technology, as evidenced by recent studies demonstrating its efficacy in specific clinical scenarios. Future research should address the gaps in understanding the long-term impacts of $ECCO_2R$, optimizing the technology for broader use cases, and overcoming barriers to its widespread adoption. Clinical trials are essential to establish stronger evidence bases for its use in different respiratory conditions and to refine the protocols for its integration into standard care practices. As ECCO$_2$R technologies become more integrated into clinical practice, they promise to improve patient outcomes and quality of life by offering more effective and less invasive alternatives to traditional respiratory support methods. Continued innovation and research are vital to unlocking the full potential of ECCO$_2$R in transforming respiratory care.

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