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Review Article

Extracorporeal CO_2 Removal (ECCO$_2$R): Hope or Hype?

Dr Mohammad Abbas [1], Dr Mohammad Fakruddin [1], Dr Shainaz Tabassum [1], Dr Farzana Begum [2]

[1]Al Ameen Medical College, Vijayapura, 586108, India.
[2] Gulbarga Institute of Medical Sciences, Kalaburgi, 585101 India.

*Corresponding Author: Dr Farzana Begum; *khanfarzana68375@gmail.com*

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Abstract

Recent technological advancements have simplified the design of extracorporeal membrane oxygenation devices, paving the way for specialized devices dedicated to the targeted removal of carbon dioxide (CO_2) from the body. These CO_2 removal devices feature a more streamlined configuration compared to traditional extracorporeal membrane oxygenation devices, operating at lower blood flows to minimize potential complications. Experimental studies have confirmed the viability, efficacy, and safety of extracorporeal CO_2 removal, showcasing its potential benefits in human subjects.

Initially conceptualized as an adjunct therapy for individuals with severe acute respiratory distress syndrome, COPD, Status asthmaticus and pulmonary artery hypertension in COPD awaiting lung transplant this approach aimed to optimize protective ventilation strategies. More recently, the application of extracorporeal CO_2 removal has given rise to the concept of "ULTRA-Lung protective ventilation," the complete implications of which are still under exploration. Moreover, the technique has demonstrated promising outcomes in addressing exacerbated hypercapnic respiratory failure.

This review delves into the intricate details of the physiological and technical aspects of CO_2 removal therapy and its various iterations. Additionally, it presents a comprehensive survey of the existing clinical evidence, illuminating the evolving potential of this innovative approach.

Keywords: ***Carbon dioxide removal; Extracorporeal circulation; Mechanical Ventilation; Adult respiratory distress syndrome; Chronic obstructive pulmonary disease, Bronchial Asthma, Lung transplant, Pulmonary artery Hypertension, Respiratory dialysis*.**

Introduction

Respiratory failure stands as a prevalent health challenge among patients admitted to Critical Care Units. Diverse strategies have been devised to address acute respiratory failure, encompassing the use of oxygen therapy devices and mechanical ventilation [1-5].

Unfortunately, these interventions are frequently linked with significant complications such as ventilator-associated pneumonia, ventilator-induced lung injury, and diaphragmatic dysfunction.

To counter respiratory failure that proves unresponsive to conventional therapies or to avert the need for intubation and mechanical ventilation-thereby reducing associated complications-various extracorporeal techniques have been developed. Among these, Veno-venous Extracorporeal Membrane Oxygenation (V-V ECMO) is widely employed and established. V-V ECMO is utilized for treating both type 1 and type 2 respiratory failure. Notably, type 2 respiratory failure can be managed with exclusive CO_2 removal, given the greater solubility and diffusibility of CO_2 compared to O_2. Consequently, low-flow techniques such as extracorporeal CO_2 removal and micro dialysis have been innovated for type 2 respiratory failure, featuring smaller cannulas and potential cost-effectiveness [6-9].

Studies indicate that low-flow techniques are linked to fewer complications and improved mortality, facilitated by the use of smaller cannulas that enable ultra-lung-protective ventilation. However, conflicting evidence exists regarding the complications and mortality benefits associated with these techniques. Therefore, the objective of this review is to comprehensively assess existing literature and formulate recommendations based on the available evidence [10-13].

Effects of Hypercapnia

Elevated levels of carbon dioxide (hypercapnia) exert detrimental effects not only on the lungs but also on various extrapulmonary organs, notably the brain. The impact of high CO_2 includes impairments in neutrophil phagocytic activity, diminished proliferation of alveolar cells, and delayed wound healing across different types of human lung cells. Hypercapnic acidosis further hinders the resealing of cell membranes [14-16].

In addition to lung-related effects, heightened CO_2 levels have been observed to impede the clearance of alveolar edema by inhibiting the Na+ -K+ -ATPase pump through a pH-independent endocytosis process. Innate immunity is also compromised as high CO_2 levels inhibit mRNA expression and the production of inflammatory cytokines (IL-6 and TNF-α) and autophagy in alveolar macrophages [17].

Hypercapnic acidosis contributes to an increase in pulmonary vascular resistance, exacerbating pulmonary hypertension. This escalation may elevate right ventricular afterload and potentially lead to acute cor-pulmonale. Furthermore, hypercapnia negatively affects diaphragmatic function through afferent transmission [18,19].

Notably, hypercapnia induces dilation of precapillary cerebral arterioles, resulting in increased cerebral blood flow. This is of particular concern in cases of reduced intracranial compliance, where elevated global cerebral blood flow can critically raise intracranial pressure. Additionally, hypercapnic acidosis directly diminishes the contractility of cardiac and vascular smooth muscle, further contributing to its multifaceted impact on physiological functions beyond the respiratory system [20,21].

Physiology and Rationale

In critically ill patients experiencing acute hypoxemic or hypercapnic respiratory failure, mechanical ventilation is a crucial life-saving intervention. However, this treatment can lead to ventilator-induced lung injury (VILI), a condition where mechanical ventilation exacerbates or initiates lung injury [22,23]. Extensive evidence highlights that excessive transpulmonary pressure, causing heightened lung stress and strain, can result in regional alveolar overdistension or the cyclic opening and closing of distal airways, contributing to lung injury. Recent years have seen significant efforts to comprehend the pathophysiology of VILI, leading to substantial changes in ventilation management and notable enhancements in patient outcomes.

The current consensus advocates for the use of low pressures and low tidal volumes to safeguard the lungs against VILI [22,23].

Nevertheless, reducing tidal volume and inspiratory pressures can lead to respiratory acidosis, which is deemed acceptable within certain safe limits under the concept of "permissive hypercapnia." However, even with lung-protective ventilation (LPV) settings, some patients may not be fully shielded, with up to one-third displaying evidence of tidal hyperinflation and an associated risk of VILI [24].

This observation has prompted the hypothesis that further reductions in tidal volume and driving pressure could minimize VILI and enhance patient-centered outcomes. However, adopting this strategy may pose an elevated risk of life-threatening respiratory acidosis, particularly when alveolar ventilation is significantly reduced with tidal volumes equal to or less than physiological dead space. To address this challenge and enable "ultra" protective mechanical ventilation strategies to minimize VILI, there has been a growing interest in extracorporeal carbon dioxide removal ($ECCO_2R$) [25,26,27].

$ECCO_2R$ is designed to eliminate blood CO_2, mitigating the adverse effects of hypercapnia and associated acidosis, thereby offering a potential solution to enhance the safety and efficacy of ultra-protective mechanical ventilation [6,7,8,10].

Types

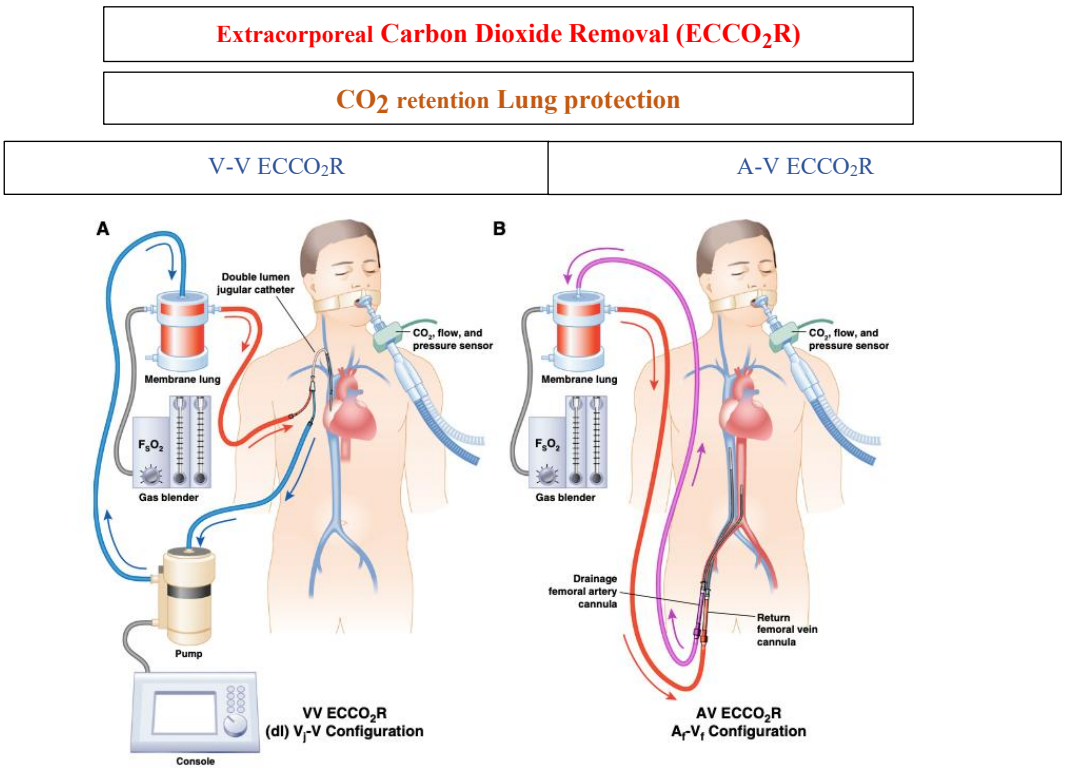
Extracorporeal CO_2 removal systems differ from ECMO. They use smaller cannula, low-blood-flow circuits and oxygenators, and predominately remove CO_2.

Circuit blood flow varies from as low as 250ml up to 3 liters per minute and such systems cannot support patients with minimal lung function or severe hypoxemia but can eliminate virtually all the CO_2 produced.

They are classified into different categories

Based on type of circuit

A. V-V-ECCo2 (Veno Venous Extracorporeal Co2 Removal)
B. A-V $ECCO_2R$ (Arteio Venous Extracorporeal Co2 Removal)



Major limitation of these devices were they need for frequent circuit substitutions (every 24 to 48 hours) because of use of polypropylene filters, this problem has been partially solved by avoiding the use of the hemofilter and using polymethyl pentene oxygenators. Recently newer technologies like Hemolung, Alung Technologies, CO_2RESET, EUROSETS S.r.l, Maquet PALP, CardioHelp, Estor ProLUNG, Hemodec DecapSmart, Novalung iLA Novalung, Novalung iLA Activve, CO_2RESET, Lilliput 2 have been developed [28-31].

Respiratory dialysis techniques with the use of hemolung devices have undergone animal trials (In Pigs) with prolific results of reduction of minute ventilation by 50% without any complications however needs further explorations among humans [7,9].

Different Extracorporeal CO_2 Removal Devices.

Device	Type and FLOW	Pump	Membrane (material)	Blood flow (l/min)
Novalung iLA Activve®	V-V- Low, medium and high flow	Diagonal rotor	poly-4-methyl-1-pentene	0.5-4.5
Novalung iLA Novalung®	A-V - Low, medium and high flow	No pump required	poly-4-methyl-1-pentene	<1.5
Maquet PALP® CardioHelp	V-V/V-A/A-V	Magnetic roller	poly-4-methyl-1-pentene	0.2-2.8
Alung Hemolung®	Low flow V-V	Centrifugal	polypropylene	0.35-0.55
Estor ProLUNG®	Low flow V-V	Peristaltic roller	poly-4-methyl-1-pentene	<0.45
Hemodec DecapSmart®	Low flow V-V	Peristaltic roller	polypropylene	<0.4
ProLUNG® system	Low flow V-V	-	poly-4-methyl-1-pentene	<0.45
PrismaLung+ and PrisMax (Involves PrismaLung + and CRRT)	Low flow V-V	-	polymethylpentene	<0.25-3
CO_2RESET	MEDIUM FLOW	-	Polymethylpentene	0.1 TO0.8
Lilliput 2	MEDIUM FLOW	Roller pump	Polymethylpentene	<2.3

Indications

$ECCO_2R$ has been studied in various pulmonary diseases leading to hypercapnic Respiratory failure, eg, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), and asthma, and as a bridge to lung transplant [32-35].

1. Rationale of $ECCO_2R$ in ARDS

a. Pathophysiological rationale of the use of $ECCO_2R$ in ARDS

The recognition of ventilatory-induced lung injury (VILI) has resulted in significant changes in the management of ventilatory support for these patients. A landmark trial conducted by the ARDSNet group demonstrated that using a low tidal volume (VT) of 6 mL/kg (compared to 12 mL/kg) in the ventilation of ARDS patients led to a significant reduction in mortality. However, recent findings have indicated that pulmonary hyperinflation still occurs in approximately 30% of ARDS patients despite this so-called "protective" ventilation strategy. This analysis suggests that reducing the VT, even in patients with a plateau pressure (Pplat) below 30 cm H2O, can have a beneficial effect. By decreasing the VT and Pplat, the driving pressure, which has recently been identified as a major risk factor for mortality in ARDS patients, will also be reduced [22-24].

However, it is important to note that reducing the VT to less than 6 mL/kg in order to achieve a low Pplat level may result in severe hypercapnia, which can increase intracranial pressure, cause pulmonary hypertension, decrease myocardial contractility, reduce renal blood flow, and trigger the release of endogenous catecholamines. Approximately two-thirds of moderately severe-to-severe ARDS patients can benefit from ultra-low tidal volume ventilation. However, 6% may develop acute cor pulmonale and 32% may experience severe acidosis with pH below 7.15. Despite reducing driving pressure by 4 cmH2O, this approach causes temporary severe acidosis. Therefore, it is not feasible for most ARDS patients on conventional invasive mechanical ventilation (IMV). Therefore, $ECCO_2R$ could be used to achieve a VT < 6 mL/kg, thus lowering the Pplat, driving pressure and mechanical power while maintaining $PaCO_2$ and pH in physiological standards [23-27].

b. Evidence of $ECCO_2R$ in ARDS and COVID 19

During the recent round table discussion among European experts on $ECCO_2R$, a consensus was reached regarding the primary objective of $ECCO_2R$ therapy in patients with ARDS and Covid Pneumonia. The focus was on implementing ultraprotective lung ventilation by effectively managing CO_2 levels. The key criterion for introducing $ECCO_2R$ was the optimization of driving pressure through plateau pressure. For patients with ARDS who underwent $ECCO_2R$, the main targets included maintaining a pH level above 7.30, a respiratory rate below 25 or 20 cycles per minute, a plateau pressure below 25 cmH2O, and a driving pressure below 14 cmH2O. Furthermore, Goligher et al. conducted a study using data from the SUPERNOVA trial, which involved 95 patients with early moderate ARDS. They assessed the independent effects of alveolar dead space fraction (ADF), respiratory system compliance (Crs), hypoxemia (PaO_2/FiO_2), and device performance (higher vs lower CO_2 extraction) on the extent of reduction in tidal volume (Vt), driving pressure, and mechanical power permitted by $ECCO_2R$. The findings demonstrated that patients with higher ADF or lower Crs, as well as those treated with higher CO_2 extraction, were more likely to benefit from $ECCO_2R$ [36,37].

Multiple studies have shown that $ECCO_2R$ effectively removes CO_2 and supports low tidal volume mechanical ventilation strategies. However, it is important to note that these studies did not assess the impact on patient-centered outcomes. Future research should investigate if incorporating a lower respiratory rate with $ECCO_2R$ improves outcomes [38,39].

The concept of combining continuous renal replacement therapy (CRRT) and $ECCO_2R$ with extremely low blood flow holds great promise. However, the potential of $ECCO_2R$ with very low blood flow to enable protective ventilation is severely restricted [7,9].

2. Role of $ECCO_2R$ in COPD

COPD is characterized by frequent exacerbations leading to repeated hospital admissions. This progressive ailment manifests with a persistent worsening of baseline CO_2 levels over its course. The retention of CO_2 is linked to the exacerbation of pulmonary arterial hypertension, contributing to increased morbidity and mortality. Therapeutic interventions such as non-invasive ventilation (NIV) are commonly employed to mitigate these complications. Maintaining normal CO_2 levels is predicted to improve both morbidity and mortality while sustaining respiratory drive. Accelerating weaning of Mechanical Ventilations (MV) in these patients, or avoidance of MV altogether, promises to reduce ICU length of stay, ultimately reducing hospital costs [1-5].

Extracorporeal carbon dioxide removal ($ECCO_2R$) has been a subject of extensive investigation to address acute increases in CO_2. Pisani et al. conducted a proof-of-concept study on $ECCO_2R$ in COPD patients experiencing chronic hypercapnia unresponsive to NIV. Their findings suggested that $ECCO_2R$ is a safe treatment option with a demonstrable effect on CO_2 reduction. The prospect of further studies with carefully selected and characterized patient groups, including assessments of lung mechanics and ventilatory drive, holds promise. Investigating response mechanisms and, crucially, incorporating patient-related outcome measures in comparison to daytime or nocturnal NIV would be particularly valuable [33].

Considering these factors, it is conceivable that, with technological advancements, $ECCO_2R$ may find its place in the future management of a specifically chosen cohort of stable advanced COPD patients.

In a retrospective study by Mathilde Azzi et al., 51 acute exacerbation COPD patients who didn't respond to non-invasive ventilation (NIV) were examined. Extracorporeal carbon dioxide removal ($ECCO_2R$) notably enhanced pH and $PaCO_2$, enabling 85% of patients to avoid intubation with lower complication rates than invasive mechanical ventilation (IMV). Despite seven major bleeding events, three leading to premature $ECCO_2R$ termination, the overall study favored $ECCO_2R$ use. There are many case reports showed favoring the of use of $ECCO_2R$ in preventing intubations and improved outcomes [34,40-42].

Currently, the randomized controlled trial "Extracorporeal CO_2 Removal with the Hemolung RAS for Mechanical Ventilation Avoidance During Acute Exacerbation of COPD (VENT-AVOID)" (NCT03255057) is underway to address the question of whether extracorporeal CO_2 removal using the Hemolung RAS can help avoid mechanical ventilation during acute exacerbation of COPD.

Christian Karagiannidis studied Veno-venous extracorporeal CO_2 removal on patients pulmonary hypertension in acute exacerbation of severe COPD (PALPTM-COPD Trial) a case series, veno-venous extracorporeal carbon dioxide removal (vv-$ECCO_2R$) has shown the ability to rapidly correct respiratory acidosis by reducing elevated $PaCO_2$ levels. Additionally, it significantly decreases mean pulmonary artery pressure (PAP) values in severe chronic obstructive pulmonary disease (COPD). This finding is crucial, as it addresses the adverse effects of acute pulmonary hypertension in respiratory failure. Further studies are needed to systematically explore vv-$ECCO_2R$'s impact on right heart function in severe COPD exacerbations requiring mechanical ventilation for respiratory acidosis management [43].

3. Role of $ECCO_2R$ while awaiting lung transplantation

It is a widely recognized fact that patients who experience acute gas exchange impairment and require invasive mechanical ventilation (IMV) while awaiting lung transplantation have a higher likelihood of mortality compared to patients who do not require IMV. The utilization of extracorporeal carbon dioxide removal ($ECCO_2R$) in such patients serves the purpose of potentially avoiding the need for endotracheal intubation and IMV, thereby minimizing the adverse effects associated with these interventions, such as ventilator-associated pneumonia, which could hinder the transplantation process. Furthermore, the implementation of $ECCO_2R$ allows for the avoidance of analgo-sedation, enabling patients to maintain the strength of their respiratory muscles and engage in active physiotherapy [44].

4. Role of $ECCO_2R$ in Status Asthmaticus

The pathophysiology of hypoxemia and hypercapnia in acute asthma is due to low ventilation/perfusion mismatch, shunting and hypoventilation. However, in cases of life-threatening dynamic hyperinflation due to status asthmaticus, ECMO is considered a salvage therapy.

Bianca J. Bromberger et al conducted study in patients with status asthmaticus complicated by refractory hypercapnia, barotrauma, or hemodynamic compromise can be effectively managed through Veno-Venous Extracorporeal Carbon Dioxide Removal (VV $ECCO_2R$). In the largest series published to date, they demonstrated that these individuals can achieve remarkably high survival rates with notably low complication rates. Furthermore, findings showcase the practicality of early extubation during $ECCO_2R$, offering the potential to further decrease complications and enhance overall patient outcomes. Given the estimated 7% mortality rate in patients necessitating invasive mechanical ventilation for severe asthma, the use of $ECCO_2R$ in such cases emerges as a secure and efficacious approach for supporting patients on their path to recovery [45].

Contraindications

Absolute	Relative
Severe coagulopathy and bleeding	Local site infection
Irreversible multiorgan dysfunction	Extremes of age
Irreversible Lung pathology and Contraindication for Lung transplants	Sepsis
Advanced Malignancies, Terminal diseases	Immunocompromised Individual

Complications [28,46]

Complications related to cannulation of $ECCO_2$ Device	Bleeding, Thrombosis of vascular access
	Infection of the insertion site
	Pneumothorax, Hematoma
	Local tissue damage, Arterial puncture and nerve injuries
	Distal ischemia (arteriovenous A-V $ECCO_2R$)- 4% to 10%
Complications after initiation (Circuit related)	Console failure
	Membrane CO_2 removal failure

	Thrombosis in the circuit/membrane
	Gas embolism
Complications related to patients and Extracorporeal run	Worsening of hypoxemia during the establishment of ultraprotective ventilation
	Bleeding in relation to anticoagulation (40%)
	Hemolysis (2% to 11%), thrombocytopenia (HIT)- 2% to 13%
	Infection, Sepsis
	Acute kidney injury, Acute Liver Injury

Conclusion

Extracorporeal CO_2 Removal ($ECCO_2R$) operates at lower blood flow rates than ECMO due to rapid diffusibility of CO_2 in blood. This allows for smaller access cannulas and simplified care, making $ECCO_2R$ potentially suitable for use in all ICUs.

$ECCO_2R$ has shown to enable ultra-lung protection in ARDS and COVID-19 pneumonia patients who fail conventional Lung protective ventilation. In addition, $ECCO_2R$ can successfully facilitate weaning of MV in COPD patients or prevent the need of intubation in COPD patients failing NIV. It has also showed improved hemodynamics and gas exchange among patients with pulmonary artery hypertension in COPD.

In patients with status asthmaticus, $ECCO_2R$ demonstrated improvements in arterial blood pH and partial pressure of carbon dioxide, facilitating a reduction in ventilator inflation pressures. Furthermore, the initiation of $ECCO_2R$ was associated with a significant decrease in the use of vasopressors.

$ECCO_2R$ has proven effective in preventing the early need for intubation in patients awaiting lung transplants with hypercapnic respiratory failure.

Overall showed improved morbidity and mortality lesser duration of mechanical ventilation, ICU stays despite of bleeding as major complications however, not enough data has been collected to determine if the therapy is universally safe and effective in this population. Due to the recent increase in awareness and use of $ECCO_2R$ several companies have produced various devices specifically for its use in humans. As an alternative to gaseous $ECCO_2R$, researchers have investigated the removal of CO_2 in the bicarbonate form in-terms of Respiratory dialysis which showed promising results in animal studies however, this investigative therapy has not yet been implemented in ICUs.

$ECCO_2R$ has shown to be an emerging clinical treatment, and continued use and research into the therapy could revolutionize hospital care for respiratory failure.

Declarations

Ethics approval and consent to participate

Not Applicable

Acknowledgement

None

Data Availability

All data are available on responsible request from the responsible author.

Conflict of interest

There is no conflict of interest.

Consent for publications

Not Applicable

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