



Cardiac Critical Care Review Article

Extracorporeal Membrane Oxygenation Carbon Dioxide Removal

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ABSTRACT

Protective lung ventilation is the mainstay ventilation strategy for patients on extracorporeal membrane oxygenation (ECMO), as prolonged mechanical ventilation increases morbidity and mortality; the technicalities of ventilation with ECMO have evolved in the last decade. ECMO on the other end of the spectrum is a complete or total extracorporeal support, which supplies complete physiological blood gas exchanges, normally performed by the native lungs and thus is capable of delivering oxygen (O₂) and removing CO equal to the metabolic needs of the patient, it requires higher flows, is more complex, and uses bigger cannulas, higher dose of heparin and higher blood volume for priming. This review describes in detail carbon dioxide removal on ECMO.

Keywords: ECMO, Carbon-dioxide removal, Protective lung ventilation, low flows on ECMO

INTRODUCTION

Protective lung ventilation is the mainstay ventilation strategy for patients on extracorporeal membrane oxygenation (ECMO), as prolonged mechanical ventilation increases morbidity and mortality; the technicalities of ventilation with ECMO have evolved in the last decade. Ventilator-associated lung injury augments multiorgan failure on ECMO and this is a dreaded scenario. The National Institute of Health showed in the year 2000 that ventilating patients on ECMO with a tidal volume (TV) of 6 mL/kg with a maximum end-inspiratory plateau pressure of 30 cm H₂O instead of 12 mL/kg VT decreased the mortality by 80%.^[1] However, even after this scenario, there was a generalized under use of protective ventilatory strategies on ECMO because of the presence of “hypercapnia.” Even with low TVs of ventilation, lung hyperinflation still occurred in about 30% of ARDS patients even with correct ventilation of ARDS net strategy. The idea of partial support ventilation has been proposed in the 1970’s by Kolobow *et al.*^[2,3] and Gattinoni *et al.*^[4] The latter suggested that applying only a few ventilator breaths at low volumes and low peak inspiratory pressures (lung rest) could prevent damage to the compromised lungs. These authors used renal replacement therapy by adding to the circuit an oxygenator and proposed the concept of removing “only a portion of carbon dioxide (CO₂) production” to allow less traumatic ventilator settings. Thus “disconnecting” oxygenation from cardiac output (CO) clearance may minimize or prevent ventilator-induced lung injury is the basic concept of extracorporeal CO₂ removal.

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ECMO PHYSIOLOGY FOR EXTRACORPOREAL CARBON DIOXIDE REMOVAL (ECCO₂R)

Renal replacement is the simplest mode of providing mechanical renal support as it provides very low blood flow. CO₂ extraction at this low flow with low primer volumes and using a coaxial catheter is removed but at very low levels.^[5,6] ECMO on the other end of the spectrum is a complete or total extracorporeal support, which supplies complete physiological blood gas exchanges, normally performed by the native lungs and thus is capable of delivering oxygen (O₂) and removing CO equal to the metabolic needs of the patient, it requires higher flows, is more complex, and uses bigger cannulas, [Table 1] higher dose of heparin and higher blood volume for priming.

INTERMEDIATE COMPLEXITY MECHANICAL SUPPORT

The intermediate complexity of mechanical support is partial extracorporeal support (ECCO₂R) which uses a 14 fr coaxial catheter to allow a blood flow of 0.3–0.5 L/min, using a roller occlusive pump which is designed to decrease hemolysis, the flow source is at a rate 6–8 L/min. Some devices include a hemofilter with the oxygenator, to allow the extraction of plasmatic water which is then infused in the circuit to prevent blood clotting.^[7] This reduces the hematocrit. Instead a centrifugal pump is an alternative, which creates a radial flow through an annual fiber oxygenator. Both can be used in venovenous (VV) ECCO₂R systems and remove up to 25% of CO₂ and transfer maximally 10 mL/min of O₂. Low dose of heparin (4–18 L/min) is used to avoid clotting.^[8]

DESCRIPTION OF ECCO₂R SYSTEMS

Early VV-ECCO₂R

In 1976, Kolobow *et al.* began to explore the possibility of treating severe respiratory failure using low frequency positive pressure ventilation alongside ECCO₂R (LFPPV-

ECCO₂R) and in 1977, they demonstrated that O₂ uptake and CO₂ removal could be dissociated in sheep. The circuits that they used were effectively VV ECMO circuits run at lower flow rates. They required a high level of anticoagulation and two surgically inserted large bore cannula, so bleeding was a major complication with mean daily transfusion requirements reported to be around 3.7–4.0 liters. The initial clinical trial of LFPPVECCO₂R showed promise but a subsequent randomized and controlled trial failed to demonstrate a survival benefit.

ARTERIOVENOUS (AV)-ECCO₂R

The concept of arterial venous pressure difference driving an ECCO₂R system was considered at an early stage in ECCO₂R development, but it only became a feasible treatment option with the advent of low resistance (10 mm Hg/2 L/min) poly-methylpentene membranes. The first clinical study of AV-ECCO₂R commenced in 1975 and the first commercially available AV-ECCO R system was released in 2002 (iLA Membran ventilator, Novalung GmbH, Hechingen, Germany). AV-ECCO R is by far the most widely used ECCO₂R technique to date [Figure 1].

METHODOLOGY OF AV-ECCO₂ SYSTEM

AV-ECCO₂R systems involve the insertion of a gas exchange membrane across an AV shunt. The gas exchange membrane is connected to O₂ which acts as a “sweep gas” to remove CO₂ that has diffused out of the patient’s blood. The flow rate of O₂ is increased in a step-wise fashion up to a maximum of 12 L/min. The shunt is usually created between the femoral artery and the contralateral femoral vein using a percutaneously inserted cannula. If necessary, unilateral placement is possible, as is pronging a patient with the device in situ. A well-designed study by Muller *et al.*^[6] demonstrated that:

- The primary determinants of blood flow through the system are: the dimensions of the cannula (in accordance with the HagenPoiseuille equation), the AV pressure gradient (rather than CO), and the resistance of the membrane.

Table 1: Extracorporeal support techniques low flow carbon dioxide removal system and ECMO compared.

Renal support (CVVH) VV	Partial extracorporeal support (ECCO ₂ R)		Total Extracorporeal support (ECMO)	
	VV	AV	VV	AV
O ₂ transfer (mL/min)	- 10	20-60	140-340	340
CO ₂ extraction (% of baseline)	- 25	50	>50	>50
Vascular access (F)	VV shunt VV shunt Double-lumen	VV shunt Double-lumen	VV femoral shunt V: 15	VV shunt AV Shunt V: 16
Needs for heparin (IU/min)	4-12	4-18	3.5-10	10-20
Approximate priming volume of circuit	2,000 mL	350 mL	500 mL	10-20

ECCO₂R: Extracorporeal carbon dioxide removal, ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, AV: Arteriovenous

- The rate of CO₂ removal depends on: Blood flow through the system, sweep gas flow, the partial pressure of CO₂ (PaCO₂) in the blood supplying the device, and the properties of the membrane (in accordance with Fick's law of diffusion).

LIMB ISCHEMIA IS DREADED COMPLICATION ON AV-ECCO₂R

The most significant complication of AV-ECCO₂R is limb ischemia caused by mechanical obstruction to arterial flow and the “steal” effect caused by blood being diverted through the artificially created shunt. The risk of ischemia is therefore related to the diameter of the arterial cannula. Reducing the diameter of the cannula has to be balanced against the effect on flow, but Novalung has reduced the recommended gauge of the arterial cannula to 13F (if the internal arterial diameter is 5.2–6 mm) or 15F (if the internal arterial diameter is more

than 6 mm). It is also recommended that ultrasound is used to ensure that the arterial lumen is at least 1.5 times the size of the arterial cannula.

MODERN VV-ECCO₂R

The most recent development in ECCO₂R technology has been a return to VV-ECCO₂R systems. However, modern VV ECCO₂R systems are very different from the VV systems used in the 80s and 90s [Table 2]. Their configuration is similar to that of a hemofilter, with a double lumen venous cannula connected to a VV circuit driven by a pump. This removes the potential for complications related to an arterial cannula and means that the system is not dependent on the patient's heart to generate a pressure gradient. However, the pumped system has the potential to trigger more of an inflammatory response and to cause more hemolysis than a pumpless system. There are currently two commercially available VV-ECCO₂R systems, each with their own characteristics.

TWO CURRENTLY AVAILABLE VV-ECCO₂R SYSTEMS ARE USED ACTIVELY

- Decap (Hemodec, Salerno, Italy) was the first modern VV-ECCO₂R system to be produced. It is a roller-ball pumped system that runs at flow rates of up to 400 mL/min. The circuit also contains a hemofilter, which according to the manufacturers “allows complete control over the lung kidney interaction in multiple organ failure patients.” An initial animal study in 2006 demonstrated no adverse events and a 20% of reduction in CO₂ using a flow rate of around 5% of the CO.^[9] Its use has since been reported in two small clinical studies^[10,11] and a case report^[12] with promising results



Figure 1: Arteriovenous-extracorporeal carbon dioxide removal (Novalung iLA).

Table 2: Comparison of different ECCO₂R system.

	Early VV-ECCO ₂ R	AV-ECCO ₂ R	Modern VV-ECCO ₂ R
Vascular access	Surgically inserted large bore venous cannula (x ²)	Percutaneous arterial (13–15F) and venous (15–17F) cannula	Percutaneous double lumen venous cannula. Decap: 14F iLA Activve: 18–24 F
Approximate priming volume of circuit	2,000 mL	350 mL	500 mL
Membrane properties	Silicon 8 m ²	PMP 1.3 m ²	PMP Decap: –0.33 m ² iLA Activve: –1.3 m ²
Approximate flow rates	2–4 L/min	1–2 L/min	Decap<0.5 L/min iLA Activve variable (0.5–4.5 L/min)
Target APTR	2–2.5	1.5–2	1.1–1.7
Other comments	Uncertain benefits and large amounts of blood loss	Significant complications related to arterial cannula	Lack of supporting evidence at present (only recently introduced)

PMP: Poly-methylpentene, ECCO₂R: Extracorporeal carbon dioxide removal

- iLA Active (Novalung, Germany): The other modern VV system available is the iLA Active (Novalung, Germany) which has the capacity to run at low or high flow rates (0.5–4.5 L/min). Its use has yet to be reported in the literature but there are plans for a randomized and controlled trial in 2013 patients (“REST” trial). Nova lung promotes the iLA Active as “the all-rounder: The VV system that covers the full range of respiratory support from highly effective CO₂ elimination to complete oxygenation.” It uses a centrifugal pump which in theory should cause less hemolysis than a roller head pump, although hemolysis has not been reported as a problem with the Decap system. Another significant difference between these two VV systems is the size of double lumen venous catheter required:

The Decap system can be used with a 14F catheter, although in the study by Terragni *et al.*^[10] The 14F dual lumen catheter had to be replaced by two 8F single lumen catheters in 3/10 patients to achieve flow rates of 400 mL/min. Novalung produces three sizes of double lumen catheter for the iLA Active ranging from 18F (optimal flow range 0.6–1 L/min) to 24F (optimal flow range 1.25–2 L/min). This suggests that two venous catheters are required to run flow rates above 2 L/min. As a comparison, the double lumen catheters that are used for hemofiltration are usually 11–14F.

MECHANISM OF ECCO₂R PHYSIOLOGY

- As the ECCO₂R system lowers the PaCO₂, the alveolar concentration of O₂ will increase in accordance with the alveolar gas equation.
- By removing CO₂, ECCO₂R allows ventilation strategies that are focused on oxygenation rather than CO₂ elimination. The previously mentioned study by Muller *et al.*^[6] looked specifically at the O₂ and CO₂ transfer that occurred through the Novalung iLA (AV-ECCO₂R) in 96 patients with ARDS. Blood samples were taken before and after the AV-ECCO₂R device to calculate the O₂ and CO₂ content of blood at these points. The flow of blood through the device was also measured and hence the rate of gas transfer could be calculated using Fick’s principle. The transfer capacity for O₂ averaged 41.7 ± 20.8 mL/min and for CO₂ was 148.0 ± 63.4 mL/min [Figures 2 and 3].

RATIONALE BEHIND THE USE OF ECCO₂R

Until recently, the primary use of ECCO₂R has been as a bridge to recovery in cases of severe hypercapnic acidosis (HCA) that are refractory to mechanical ventilation. In the vast majority of cases, this has been in the context of ARDS, although it has also been used in a variety of other situations. The threshold at which a HCA requires treatment is debatable and will vary depending on the clinical situation but most

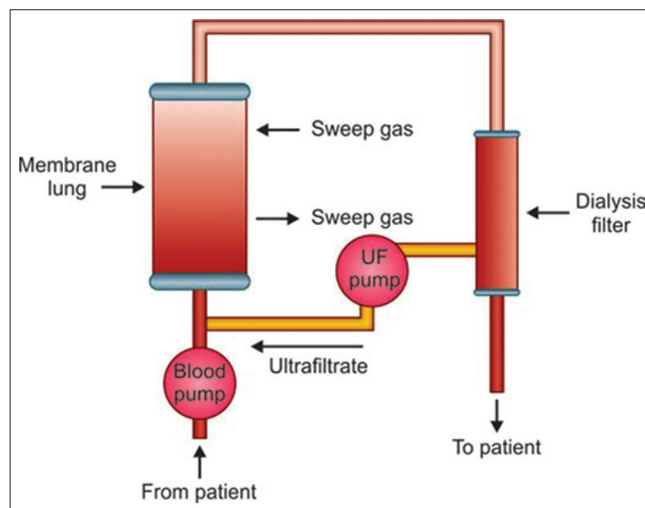


Figure 2: iLA Active; circuit diagram.



Figure 3: Blood is pumped through a membrane lung with a dialysis filter.

would agree that there comes a point at which intervention is required.

COMPLICATIONS ASSOCIATED WITH ECCO₂R

The complications of AV-ECCO₂R and VV-ECCO₂R should be looked at separately since the two configurations have different side effect profiles. The most concerning complications of AV-ECCO₂R have been related to arterial cannulation with three reports of limb ischemia requiring amputation in the early literature. Improvements in the cannulae allowed the use of shorter (9 cm vs. 14 cm) and thinner (13 vs. 15 Fr) cannulae for arterial cannulation which with the use of ultrasound to ensure that the internal diameter of the artery is of adequate size (1.5 times the external diameter of the cannula) have reduced complication rates. Hence, the complication rates in [Table 3] are from the most recent prospective study of AV-ECCO₂R.^[13]

Table 3: Complications of AV-ECCO₂R and VV-ECCO₂R.

Complications	Complications rate with AV-ECCO ₂ R	Complications rate with VV-ECCO ₂ R
Limb ischemia	5.9% (3/51)	0
Compartment syndrome	1.9% (1/51)	0
Bleeding during cannulation	1.9% (1/51)	0
Cannula thrombosis	1.9% (1/51)	16.7% (3/18)
Thrombosis of exchange membrane	Not reported	16.7% (3/18)
Pump malfunction	0	5.6% (1/18)

VV-ECCO₂R: Venovenous-Extracorporeal carbon dioxide removal, AV-ECCO₂R: Arteriovenous-Extracorporeal carbon dioxide removal

The complication rates for VV-ECCO₂R in this table are compiled from the 18 cases of its use that are reported in the literature.^[9-12,14] Plasma leakage, heparin-induced thrombocytopenia,^[15] hemolysis are some dreaded complications observed all throughout this process.^[16] There has also been a report of critical hypotension when AV-ECCO₂R was initiated in a patient who had severe hypoxia and septic shock are other complications.^[17]

DISCUSSION

Worku *et al.* in recent times post-COVID-19 have discussed that driving pressure below conventionally accepted limits of ultra-protective targets can further improve patient centered outcomes compared with standard low-volume and low-pressure ventilation strategies.^[18] Ventilator parameters under ECCO₂R largely conformed with ultra-protective ventilation targets from a mechanical perspective (driving and plateau pressures).^[19] Plateau pressure was ≥ 25 cm H₂O in all 10 cohorts at the outset and was reduced significantly at 24 h with reported values ≤ 25 cm H₂O in seven studies. Driving pressure was >14 cm H₂O in just two of the seven studies reporting ΔP at baseline. While it was reduced to <10 cm H₂O in five studies, and below 14 cm H₂O in all reporting studies, TV remained slightly above 4 mL/kg in the majority.^[20-25]

ECCO₂R is rightly referred to as a low-flow ECMO.^[26] ECCO₂R was originally developed to reduce the intensity of mechanical ventilation in patients with acute hypercarbic respiratory failure. There remains an unmet need to better quantify lung injury and to identify patients who may benefit most from a reduction in the intensity of mechanical ventilation. Current evidences do not exclude the possibility to smaller beneficial effects to a subset of patients. At present, as per most recent reviews and studies, ECCO₂R should not be used outside of a research clinical trial or only in highly selected cases.^[27]

CONCLUSION

VV ECCO₂R supported significant reductions in driving pressure at 24 h in moderate-to-severe ARDS, with an overall

mortality of 41.6%. While early ECCO₂R may facilitate ultra-protective ventilation and mitigate ARDS progression, the benefits are currently offset by the invasiveness of therapy, and limited CO₂ removal made possible at low blood flow rates. Significant reductions in respiratory rate may emerge as the key sub-component of mechanical power; hence, reductions in ergotrauma may not be feasible when using very low blood flow rates, potentially limiting the utility of ECCO₂R in patients with more severe forms of ARDS, or right ventricular dysfunction. Enrichment of study populations, and reporting data consistently to minimum standards, is critical to meaningfully researching benefits of ECCO₂R therapy in ARDS. From renal to pulmonary dialysis, new techniques rise to assist clinicians in the management of critical patients with organ failures. Coupling mild extracorporeal support devices with ultra-protective ventilation represent the most promising possibility to obtain the best therapeutic goals in the severe ARDS patients' treatment. New strategies for ventilation support are currently under investigation, specifically for the treatment of COPD exacerbations and as a bridge for lung transplant.

Declaration of patient consent

Patient's consent not required as their identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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