

Extracorporeal carbon dioxide removal (ECCO₂R) in respiratory failure: an overview, and where next? 2C04 3A13

A Baker, D Richardson, G Craig

Extracorporeal carbon dioxide removal (ECCO₂R) is used to facilitate protective ventilation strategies and to treat severe hypercapnic acidosis that is refractory to mechanical ventilation. There is an increasing amount of interest in the use of ECCO₂R but there are no recommendations for its use that take the most recent evidence into account. In 2008, the National Institute of Health and Clinical Excellence (NICE) published guidelines on 'Arteriovenous Extracorporeal Membrane Carbon Dioxide Removal'.¹ However, since that time there have been a number of studies in the area and some significant technological advances including the introduction of commercially available VV-ECCO₂R systems. The aim of this article is to provide an overview of ECCO₂R, review the literature relating to its use and discuss its future role in the intensive care setting.

Keywords: extracorporeal carbon dioxide removal; respiratory failure; hypercapnic acidosis

Introduction

ECCO₂R refers to the process by which an extracorporeal circuit is used for the primary purpose of removing CO₂ from the body, thereby providing partial respiratory support. There are various ways to classify ECCO₂R systems but for the purpose of this review it will be classified as shown in **Figure 1**.

Description of ECCO₂R systems

Early VV-ECCO₂R

In 1976, Kolobow and Gattinoni began to explore the possibility of treating severe respiratory failure using low frequency positive pressure ventilation alongside extracorporeal CO₂ removal (LFPPV-ECCO₂R) and, in 1977, they demonstrated that oxygen uptake and CO₂ removal could be dissociated in sheep.² The circuits that they used were effectively venovenous ECMO circuits run at lower flow rates. They required a high level of anticoagulation and two surgically inserted large bore cannulae, so bleeding was a major complication with mean daily transfusion requirements reported to be 3.7 litres.³

The initial clinical trial of LFPPV-ECCO₂R showed promise⁴ but a subsequent randomised controlled trial failed to demonstrate a survival benefit.³

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/2L/min) polymethylpentene (PMP) membranes. The first clinical study of AV-ECCO₂R commenced in 1997⁵ and the first commercially

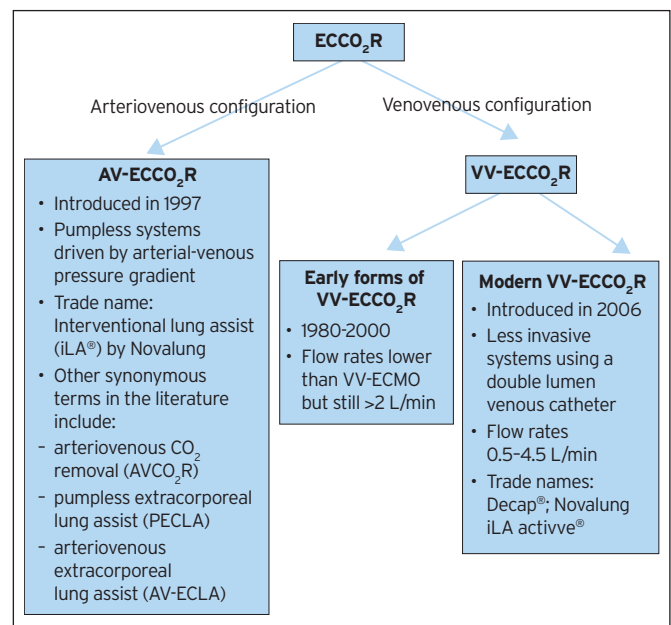


Figure 1 Classification of ECCO₂R systems

available AV-ECCO₂R system was released in 2002 (iLA Membranventilator®, Novalung GmbH, Hechingen, Germany). AV-ECCO₂R is by far the most widely used ECCO₂R technique to date (**Figure 2**).

AV-ECCO₂R systems involve the insertion of a gas exchange membrane across an AV shunt. The gas exchange membrane is connected to oxygen which acts as a "sweep gas" to remove CO₂ that has diffused out of the patient's blood. The flow rate of oxygen is increased in a stepwise fashion up to a maximum of 12 L/min. The shunt is usually created between the femoral

	Early VV-ECCO ₂ R	AV-ECCO ₂ R	Modern VV-ECCO ₂ R
Vascular access	Surgically inserted large bore venous cannulae (x2)	Percutaneous arterial (13-15F) and venous (15-17F) cannulae	Percutaneous double lumen venous cannula Decap®: 14F iLA Activve®: 18-24F
Approximate priming volume of circuit	2,000 mL	350 mL	500 mL
Membrane properties	Silicon 8 m ²	PMP 1.3m ²	PMP Decap® - 0.33m ² iLA Activve® - 1.3m 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 benefit and large amounts of blood loss	Significant complications related to arterial cannula	Lack of supporting evidence at present (only recently introduced)

Table 1 Comparison of different ECCO₂R systems.



Figure 2 AV-ECCO₂R (Novalung iLA®) (courtesy of Inspiration Healthcare Limited).

artery and the contralateral femoral vein using a percutaneously inserted cannula. If necessary, unilateral placement is possible, as is proning 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 cannulae (in accordance with the Hagen-Poiseuille equation), the arteriovenous pressure gradient (rather than cardiac output), and the resistance of the membrane.
- The rate of CO₂ removal depends on: blood flow through the system, sweep gas flow, the partial pressure of CO₂ in the blood supplying the device and the properties of the membrane (in accordance with Fick's law of diffusion).

AV-ECCO₂R effectively creates an extravascular bed. This reduces systemic vascular resistance and a compensatory increase in cardiac output is required to maintain blood pressure. Patients with cardiac failure may not be able to achieve this and are excluded from almost all of the studies using AV-ECCO₂R.

Another important cardiovascular consideration regarding the use of AV-ECCO₂R is that the proportion of the cardiac output that flows through the ECCO₂R system is not involved

in peripheral perfusion, hence the patient's effective cardiac output is reduced. Furthermore, as systemic vascular resistance increases relative to cardiac output, a larger proportion of the cardiac output will be 'lost' through the shunt.

The modern generation of ECCO₂R systems have a heparinised coating which reduces the degree of anticoagulation required (Novalung recommend targeting a partial thromboplastin time of 55 seconds). AV-ECCO₂R has been used without anticoagulation and blood flow through the circuit did not seem to be compromised,^{7,8} however, it is still recommended that the patient is systemically heparinised.

The most significant complication of AV-ECCO₂R is limb ischaemia caused by mechanical obstruction to arterial flow and the 'steal' effect caused by blood being diverted through the artificially created shunt. The risk of ischaemia 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 have 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 venovenous systems used in the 80s and 90s (**Table 1**). Their configuration is similar to that of a haemofilter, with a double lumen venous cannula connected to a venovenous 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 haemolysis than a pumpless system. There are currently two commercially available VV-ECCO₂R systems, each with their own characteristics:

1. 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 haemofilter, 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% reduction in CO₂ using a flow rate of around 5% of the cardiac output.⁹ Its use has since been reported in two small clinical studies^{10,11} and a case report¹² with promising results.
2. The other modern venovenous system available is the iLA Activve® (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 randomised controlled trial in 2,013 patients ('REST' trial). Novalung promote the iLA Activve® as 'The All-Rounder: The venovenous system that covers the full range of respiratory support from highly effective carbon dioxide elimination to complete oxygenation.' It uses a centrifugal pump which in theory should cause less haemolysis than a roller-head pump, although haemolysis has not been reported as a problem with the Decap® system. Another significant difference between these two venovenous 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* the 14F dual lumen catheter had to be replaced by two 8F single lumen catheters in 3/10 patients in order to achieve flow rates of 400 mL/min.¹⁰ Novalung produce three sizes of double lumen catheter for the iLA Activve® 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 haemofiltration are usually 11-14F.

This review will focus on AV-ECCO₂R and modern VV-ECCO₂R systems.

ECCO₂R gas exchange physiology

CO₂ removal

Theoretically, an ultra-efficient ECCO₂R system could eliminate all the CO₂ that the body produces with flow rates of just 0.5 L/min, because a litre of blood with a PaCO₂ of 5 kPa contains around 500 mL of CO₂ and the body produces approximately 250 mL/min.

Oxygenation

The potential for ECCO₂R systems to oxygenate blood is much more limited since there is effectively a limit to the amount of oxygen that a given volume of blood can carry. Only a few millilitres of oxygen can be added to a litre of well-saturated arterial blood and only around 35 mL of oxygen can be added to a litre of venous blood (assuming SaO₂=75% and Hb=100g/L) (see **Figure 3**).

Therefore, in order to provide the body's oxygen requirements of 250 mL/min the extracorporeal flow rate would have to be at least 6 L/min for a venovenous system and

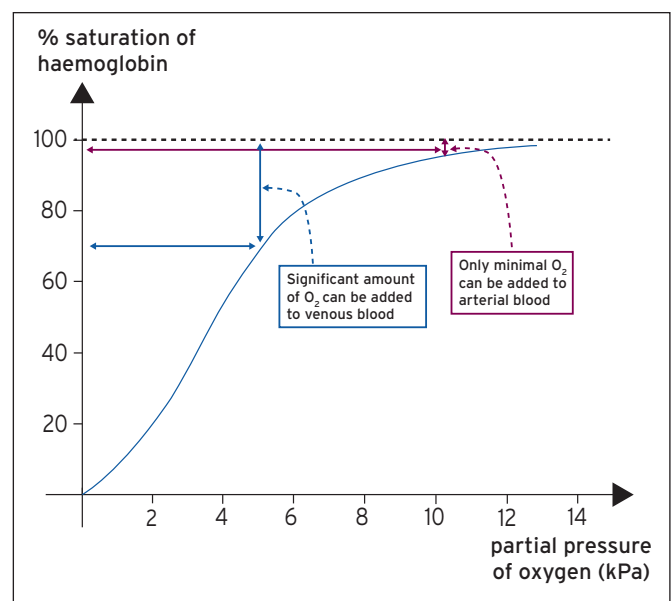


Figure 3 Oxyhaemoglobin dissociation curve illustrating why AV-ECCO₂R can only make a small contribution to oxygenation.

many times this for an arteriovenous system. This explains why the iLA Activve® has the potential to oxygenate as well as remove CO₂ (it is a venovenous system that can run at high flow rates).

In clinical practice, ECCO₂R often exceeds expectations with regards to oxygenation, which can be explained by two other factors:

1. As the ECCO₂R system lowers the PaCO₂, the alveolar concentration of O₂ will increase in accordance with the alveolar gas equation.
2. By removing CO₂, ECCO₂R allows ventilation strategies that are focused on oxygenation rather than CO₂ elimination.

The previously mentioned study by Muller *et al* looked specifically at the O₂ and CO₂ transfer that occurred via the Novalung iLA® (AV-ECCO₂R) in 96 patients with ARDS.⁶ Blood samples were taken before and after the AV-ECCO₂R device in order 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 oxygen averaged 41.7 ± 20.8 mL/min and for carbon dioxide was 148.0 ± 63.4 mL/min.

A similar study has not been yet been done to look at the gas transfer capacity of modern VV-ECCO₂R systems. However, one would expect VV-ECCO₂R systems to contribute more to oxygenation than AV-ECCO₂R systems at any given flow rate, since they receive blood with a lower oxygen content. Gas exchange would also be related to the blood flow rate which in the case of the iLA Activve can be varied from 0.5-4.5 L/min.

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

More recently, ECCO₂R has been used to allow protective ventilation in patients with acute respiratory distress syndrome (ARDS) in whom HCA has not yet become refractory and this is likely to be where its role lies in the future. It is now well established that mechanical ventilation can initiate and exacerbate lung injury. The recognised mechanisms of ventilator-induced lung injury are volutrauma (stretch injury), barotrauma (airway rupture caused by positive pressure ventilation), atelectrauma (shear injury), and biotrauma (cytokine-mediated injury). A protective ventilation strategy using lower tidal volumes is the only intervention that has convincingly been shown to reduce mortality in patients with ARDS.¹³ However, sometimes the severity of lung injury makes it impossible to stay within the limits of the ARDSNet ventilation strategy and ECCO₂R may have a role in facilitating protective ventilation in these situations. Furthermore, ECCO₂R could be used to reduce the tidal volume to less than 6 mL/kg when the plateau pressure is already less than 30 cmH₂O ('ultra-protective' ventilation). Whether or not there is any benefit to ultra-protective ventilation is debatable, but the results of two recent studies^{10,14} addressing this issue in patients with early (<72 hr) ARDS are worthy of further mention:

Study 1

Terragni *et al* used VV-ECCO₂R to facilitate 'ultra-protective' ventilation.¹⁰ They recruited 32 patients with early (<72 hr) ARDS and ventilated them according to the ARDSNet protocol for 72 hr, at which point the tidal volume was reduced from 6 to 4 mL/kg in all patients (n=10) who had a plateau pressure of between 28 and 30 cm H₂O. The rise in PaCO₂ that followed was initially treated with an increase in respiratory rate along with intravenous HCO₃⁻, but all 10 patients were eventually treated with VV-ECCO₂R. VV-ECCO₂R successfully treated the hypercapnic acidosis in all cases and allowed the protective ventilation strategy (4 mL/kg tidal volumes and higher levels of PEEP) to continue. The study also demonstrated a reduction in bronchoalveolar inflammatory cytokines (IL-6, IL-8, IL-1b, IL-Ra) after 72 hours of ventilation with 4 mL/kg but not 6 mL/kg. There did not appear to be any harmful effects relating to the ultra-protective ventilation strategy or the VV-ECCO₂R. Although this study is small and uncontrolled it suggests that there may be some benefit to an ultra-protective ventilation strategy facilitated by VV-ECCO₂R within 72 hours of diagnosing ARDS.

Study 2

Zimmerman *et al* recruited 121 patients with ARDS into a study which used an algorithm for implementing AV-ECCO₂R.¹⁴ According to the algorithm, AV-ECCO₂R was used if the patient still had a PaO₂/FiO₂ ratio <200 mm Hg and/or pH <7.25 after a 24 hour period of optimisation (ARDSNet 'high PEEP' ventilation, proning, fluid management). AV-ECCO₂R was used in 51 patients and the mean tidal volumes were reduced to 4.4 mL/kg (3.4-5.4). This was an uncontrolled study, but the authors reported a reduction in mortality in relation to a

retrospective comparator group that used AV-ECCO₂R as a rescue therapy in ARDS. Six patients (11.8%) in this study had complications relating to the use of AV-ECCO₂R.

By eliminating CO₂, ECCO₂R effectively allows the decoupling of oxygenation from CO₂ removal. A logical extension of this decoupling concept is to combine ECCO₂R with non-invasive CPAP.

Current evidence

A literature review was conducted using MEDLINE (2000-March 2011) and EMBASE (2000-March 2011). Search terms included all of the acronyms and descriptive terms for extracorporeal carbon dioxide removal systems as well as the combination of 'extracorporeal circulation' (MeSH) AND ('carbon dioxide' OR CO₂). This revealed a total of 293 citations of which only 18 were deemed relevant once case studies had been excluded. Within these 18 citations, there were no randomised controlled trials, a single health technology assessment¹⁵ and only two prospective interventional studies^{10,14} both of which have already been summarised. The remainder of the relevant literature was confined to either prospective or retrospective case series¹⁶⁻²⁴ although these do demonstrate that ECCO₂R has been used on over 500 patients (with no unifying database). Overall, there is good evidence that ECCO₂R can effectively reduce PaCO₂ and make a small contribution to oxygenation in patients with ARDS. Likewise, studies^{14,18-20,22,23} have demonstrated that ECCO₂R facilitates a lung-protective ventilation strategy by allowing a reduction in tidal volumes and inspiratory airway pressures. ECCO₂R may even complement specific forms of protective ventilation such as HFOV^{21,24} or APRV (Airway Pressure Release Ventilation) with 2-4 mL/kg tidal volumes.²¹ However, it is not possible to draw any valid conclusions about the effect of ECCO₂R on survival in patients with acute lung injury.

There are a number of reports of its use in other clinical scenarios, namely, as a bridge to transplant,^{11,25} in combined head and chest injury,^{7,8,26} in near fatal asthma,²⁷⁻²⁹ as an aid to weaning from mechanical ventilation,^{12,30} to facilitate thoracic surgery^{19,22,31} and to facilitate transfer.^{32,33} However, these are all case reports or very small case series and as such do not provide any definitive evidence of benefit.

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 ischaemia requiring amputation in the early literature. Improvements in the cannulae allowed the use of shorter (9 cm versus 14 cm) and thinner (13 versus 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) has reduced complication rates. Hence the complication rates in **Table 2** are from the most recent prospective study of AV-ECCO₂R.¹⁴ The complication rates for VV-ECCO₂R in this

Complication	Complication rate with AV-ECCO ₂ R ¹⁴	Complication rate with VV-ECCO ₂ R ^{9-12,34}
Limb ischaemia	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)

Table 2 Complications of AV-ECCO₂R and VV-ECCO₂R.

table are compiled from the 18 cases of its use that are reported in the literature.^{9,10,11,12,34}

The other complications of AV-ECCO₂R that have been reported in the literature are: plasma leakage, heparin-induced thrombocytopenia,²⁴ and haemolysis.¹⁸ There has also been a report of critical hypotension when AV-ECCO₂R was initiated in a patient who had severe hypoxia and septic shock.²⁴

It is important to mention that almost all the studies of AV-ECCO₂R exclude patients with cardiac failure; however in this selected population, AV-ECCO₂R seems to be tolerated well from a cardiovascular perspective. In fact, in the majority of cases cardiovascular parameters were unchanged or became more favorable after initiation of AV-ECCO₂R.

Conclusions

ECCO₂R is not a new concept but it is an area of expanding interest and there are an increasing number of ECCO₂R devices on the market. The quality of supporting evidence for ECCO₂R depends on both the type of ECCO₂R system and the clinical situation in which it is being used.

AV-ECCO₂R has been used fairly extensively as a rescue therapy for severe HCA in patients with ARDS. Using the GRADE approach, the level of evidence to support the hypothesis that AV-ECCO₂R improves gas exchange and allows more protective ventilation in this situation is of moderate quality.³⁵ However, conclusions cannot be drawn about whether or not there is a survival benefit, since none of the studies have control groups.

AV-ECCO₂R has been used in a number of clinical situations apart from ARDS, however, the supporting evidence is of low quality at best, making it difficult to assess the risk-benefit ratio in these areas. A lack of evidence does not completely preclude the use of an intervention such as this, particularly when the alternative is likely to result in death or irreversible brain injury. However, if ECCO₂R is used under these circumstances, it is important that it is done so under close clinical governance. It is also important that the patients or their relatives understand the uncertainty about the procedure's efficacy and the risk of complications.

One of the primary concerns around AV-ECCO₂R is the potential for arterial damage and ischaemic complications caused by the arterial cannula which makes VV-ECCO₂R an

attractive alternative. It is likely that the future of ECCO₂R will be in venovenous systems in the same way that venovenous haemofiltration surpassed its arteriovenous predecessor. This would make extracorporeal gas exchange including a limited degree of oxygenation available to most large intensive care units. However, the current published evidence base for VV-ECCO₂R is limited to a total of 18 patients.^{9-12,34}

There are two studies of VV-ECCO₂R that are currently recruiting patients. One is being carried out in Texas, looking at VV-ECCO₂R in patients with chronic obstructive pulmonary disease and acute respiratory failure (ClinicalTrials.gov identifier: NCT00594009). The other is a French study that has incorporated a neonatal oxygenator into a haemofiltration circuit and is investigating its use in patients with ARDS and acute renal failure (ClinicalTrials.gov identifier: NCT01239966). Both studies are small, uncontrolled studies looking at safety and efficiency but they could help to open the door for larger, randomised studies.

There is particular interest in the use of ECCO₂R to allow ultra-protective ventilation at an early stage of ARDS and initial studies have been promising. The results of a recently completed randomised controlled trial are awaited, in which 120 patients with early ARDS were randomised to receive either AV-ECCO₂R or standard ARDSNet ventilation (Xtravent ClinicalTrials.gov identifier: NCT00538928). There are also plans for a randomised controlled trial of VV-ECCO₂R (iLA active®) in early ARDS (REST).

In the UK, AV-ECCO₂R has started to become an accepted rescue therapy for refractory HCA and VV-ECCO₂R systems are being introduced. However, the iLA Active® currently costs around £50,000, plus disposables per patient of up to £5,000 and arteriovenous systems require a £6,000 monitor plus disposables per patient of £2,500. Hence we have a situation in which a costly invasive therapy with a limited evidence base is being used without a national data collection system or up-to-date guidelines. Most would agree that there is a role for ECCO₂R in intensive care but there are currently no clearly defined indications for its use. With the imminent introduction of venovenous systems, now would be a good time to draw a consensus on the subject and an opportunity for UK intensive care medicine to be at the forefront of establishing whether there is a cost-benefit advantage or not.

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Andrew Baker Specialist Trainee year 7, Anaesthetics and Intensive Care Medicine, Southampton General Hospital
andrewkellasker@doctors.org.uk

Dominic Richardson Consultant in Anaesthetics and Intensive Care Medicine, Southampton General Hospital

Gordon Craig Consultant in Anaesthetics and Intensive Care medicine, Queen Alexandra Hospital, Portsmouth