Extracorporeal carbon dioxide removal (ECCO₂R) has become increasingly popular in critical care over the last 5–10 years for the management of hypercapnic respiratory failure or to facilitate ultra-protective ventilation in patients with acute respiratory distress syndrome (ARDS).¹ ECCO₂R provides partial respiratory support by clearing 25%–30% of produced CO₂ from the venous blood with minimal direct impact on systemic oxygenation using blood flows of 0.5 L/min.²⁻⁴ By reducing the CO₂ needing to be cleared by the native lungs, ECCO₂R allows for a lower native pulmonary alveolar minute ventilation, an improvement in lung mechanics, and a reduction in the resistive and elastic work of breathing.¹

ECCO₂R may be used either as an adjunct or as an alternative to conventional intensive care unit supportive therapy in a range of conditions with persisting hypercapnia. It is important to appreciate the impact of ECCO₂R on: 1) work of breathing; 2) maximal CO₂ removed; 3) interactions with the native lung; 4) control of the respiratory drive in awake patients; 5) potential complications of ECCO₂R, particularly bleeding and thrombosis; 6) modifications in management that are necessary once the patient is established on ECCO₂R.

This review will focus on exploring how the devices clear CO₂, the impact of ECCO₂R on the native pulmonary physiology, and systemic gas exchange. Finally, we discuss the modifications to patient management required while on ECCO₂R.

Gas exchange across the membrane

ECCO₂R membranes enable gas exchange in a manner analogous to the native lung.⁵ Modern hollow-fibre membranes are constructed of polymethylpentene (PMP) or siloxane.⁶ There is a capillary network within the membrane allowing a flow of gas and blood through separate channels and gases to move down their concentration gradient.⁷

CO₂ production (VCO₂) is directly related to oxygen (O₂) consumption (VO₂), through a proportionality constant called the respiratory quotient (VCO₂/VO₂), which, although usually assumed equal to 0.8, becomes variable in patients on extracorporeal support, depending on the efficiency of the membrane, the gas flow and the venous PaCO₂. The greater the CO₂ removed by the ECCO₂R device, the lower the respiratory quotient.⁸⁻¹¹

ABSTRACT

Objective: Extracorporeal venovenous carbon dioxide removal (ECCO₂R) is increasingly used to facilitate ultra-protective mechanical ventilation, or to prevent or avoid mechanical ventilation in selected patients. This review focuses on how extracorporeal devices clear CO₂, their impact on native pulmonary physiology, and systemic gas exchange. Finally, we discuss the modifications to patient management required while on ECCO₂R.

The VCO₂ of an adult at rest is about 3 mL/kg/min. CO₂ is carried in the blood in solution (5%), as carbonic acid (85%), or bound to proteins (10%) including haemoglobin. Because of its higher solubility compared with O₂, CO₂ diffuses about 20 times faster than O₂.¹² Consequently, the removal of CO₂ can occur at relatively lower extracorporeal blood flows (0.5–1 L/min) than does the transfer of clinically relevant amounts of O₂ (4–5 L/min). In a perfectly efficient system, a blood flow of 0.5 L/min would be sufficient to remove all the CO₂ produced.¹³⁻¹⁸ However, CO₂ clearance depends on the gradient between the CO₂ in the venous blood, the sweep gas CO₂, sweep gas flow rate, blood CO₂ content, pH and haemoglobin,¹⁹ as well as the efficiency of the gas exchange membrane. Blocked capillary channels in the extracorporeal lung can result in intra-membrane dead space and shunt, reducing its efficiency. These factors limit the amount of CO₂ removed from the blood and ECCO₂R is usually able to remove up to 25% of carbon dioxide production.²⁰,²¹

Blood flow through the artificial lung is analogous to the perfusion of the native lung, while the sweep gas flow rate is analogous to minute ventilation. Increasing sweep gas flow rate increases CO₂ clearance²² until a maximum blood flow/sweep gas flow ratio is reached, beyond which CO₂ removal does not increase. In clinical practice, a ventilation/perfusion ratio of 10–11:1 (5–6 L/min of gas flow for 0.5 L/min blood flow) is the point of maximal CO₂ removal.²² The relationship between CO₂ clearance and blood flow is non-linear; at low sweep flow rates, CO₂ clearance is highly sensitive to changing sweep flow rates; but at high sweep flow rates the CO₂ clearance is relatively insensitive.²²,²³
CO₂ also exhibits biphasic kinetics, with an initial rapid decline in PaCO₂ followed by a slower decline. This is caused by the rapid removal of dissolved CO₂ followed by equilibration of carbonic acid, carboxyhaemoglobin and tissue stores of CO₂.²⁴ Although, from a physiological point of view calculating the amount of CO₂ removed from the blood is essential to understanding the interaction between the artificial and the native lung, from a clinical viewpoint, the exact amount of CO₂ exchanged by the membrane is generally not measured. Rather, the sweep gas flow rate is merely changed to maintain an appropriate systemic arterial PCO₂ and work of breathing. Should CO₂ control deteriorate, although patient factors are the most likely cause, it is important to remember that microthrombi in the membrane or water accumulation on the gas side of the membrane will reduce the capacity for CO₂ diffusion.²⁵ It is also important to appreciate that often the goal of ECCO₂R is not necessarily the reduction in PaCO₂, but the control of PaCO₂ to allow a reduction in the mechanical ventilation or a reduction in work of breathing.

Impact of ECCO₂R on native lung physiology

The impact of ECCO₂R on native lung physiology is poorly understood. The most consistent effect of ECCO₂R in both clinical and pre-clinical studies is to reduce mixed venous PCO₂ and to improve arterial pH.²⁶-³¹ Associated with this reduction is a simultaneous reduction in respiratory rate and hence minute ventilation.²⁶,²⁹,³² The ultimate effect on arterial P CO₂ depends on multiple factors related to the underlying pathological process. For patients with exacerbation of chronic obstructive pulmonary disease (COPD), the reduction in respiratory rate and tidal volume that results from the reduction in the venous PCO₂ increases expiratory time, allowing a reduction in intrinsic positive end-expiratory pressure (PEEP) and end-inspiratory lung volume, improving alveolar dead space and alleviating any flattening of the diaphragm, which decreases respiratory work.³³ There are limited data available about the impact of ECCO₂R on other aspects of pulmonary physiology in clinical settings. A small pilot study reported on the changes associated with ECCO₂R in patients with COPD weaning from a ventilator and found that intrinsic PEEP, inspiratory pulmonary resistance and work of breathing were all reduced.³⁴

The intended benefits of ECCO₂R as an adjunct to ARDS are to allow a reduction in tidal volumes and respiratory rate, as well as plateau and, possibly, mean airway pressures.²⁹,³⁵-³⁸ However, in moderate or severe ARDS, ECCO₂R may have important detrimental effects on oxygenation. A reduction in tidal volumes without a significant increase in PEEP decreases the mean airway pressure (mPaw) and therefore the mean lung volume. A reduction in mPaw may lead to derecruitment, progressive atelectasis and hypoxaemia.⁸,³⁷ The effect on the PAO₂/FIO₂ ratio has been variably reported in the literature,³⁴,³⁷ likely due to clinicians altering ventilator settings, particularly PEEP.²⁶,²⁹,³⁷ Arterial hypoxaemia may be further aggravated by a reduction in hypoxic pulmonary vasoconstriction due to the improvement in mixed venous Po₂ caused by the return of oxygenated blood into the great veins, which leads to an increased native lung shunt fraction. The effect on the abolition of hypoxic vasoconstriction will depend on the venous Po₂ and the cardiac output but also the underlying lung disease. In patients with severe lung inflammation, hypoxic vasoconstriction may already be abolished and a change in mixed venous Po₂ will have little additional effect, while in patients with preserved hypoxic vasoconstriction, ECCO₂R may lead to severe hypoxaemia.²¹,³⁹-⁴¹

ECCO₂R also causes important changes in the partial pressure of alveolar gases, leading to a reduction of alveolar Po₂ (PAO₂) and alveolar nitrogen. Alveolar nitrogen reduces because the gradient between the nitrogen in the alveoli and the nitrogen in the blood returned from the artificial lung favours its diffusion out of the alveoli, with consequent reabsorption atelectasis. The reduction in PAO₂ is due to a reduction in mixed venous PaCO₂ and the increase in the respiratory quotient. This leads, according to the alveolar gas equation, to a reduction in the PAO₂ if FIO₂ is kept constant.³⁹ The resultant effect could lead to a worsening of shunt fraction.

There are data to support an improvement in right ventricular function associated with the use of ECCO₂R. The effect of hypercapnia on the right ventricle has been well described. Hypercapnia, hypoxaemia, acidosis, pulmonary shunt and hypoxic pulmonary vasoconstriction all contribute to pulmonary arterial hypertension leading to increased right ventricular afterload.⁴²,⁴³ This is further compounded by the effects of high mean intrathoracic pressures secondary to positive pressure ventilation. Right ventricular contractility is reduced by the effects of hypoxaemia and acidosis on cardiac myocytes, as well as the relative ischaemia caused by increased right ventricular end diastolic pressure due to acute pulmonary hypertension. The net effect of these insults is that the right ventricle dilates and fails.⁴² As it does so, the left ventricular function reduces due to ventricular interdependence, and organs including the liver are exposed to a lower cardiac output with higher venous pressure and lower arterial pressure, resulting in organ oedema, dysfunction and ultimately failure.

The clearance of CO₂ and resolution of respiratory acidosis result in reduced pulmonary arterial pressure and improved cardiac myocyte contractility, with consequent improvement in indices of right ventricular function.⁴⁴,⁴⁵ This is manifested...
by normalisation of right ventricular cross-sectional area, improvement in right ventricular end diastolic pressure, and improvement in radial and longitudinal contractility. The improvement in right ventricular function is also associated with an overall improvement in cardiac output and left ventricular function.44,45

**Current roles for ECCO₂R**

Large randomised controlled trials have not yet been undertaken exploring the role of ECCO₂R. Observational studies and case reports have described its use in hypercapnic respiratory failure, particularly for exacerbations of COPD and as an adjunct to allow lung protective ventilation.

For ARDS, the key intervention in the ICU has been the application of lung-protective ventilation. Strategies which facilitate lung protection and have been shown to improve mortality include optimal PEEP levels;46 mechanical ventilation with plateau pressure < 30 cmH₂O and tidal volumes normalised to predicted body weight;47,48 ventilation in the prone position; and cisatracurium infusion.49-51 Those providing improved oxygenation alone (eg, inhaled nitric oxide) have not been shown to improve mortality. Patients with severe ARDS (PaO₂/FiO₂ < 13.3 kPa)52 or significant hypercapnia (pH < 7.20 due to respiratory acidosis) have a significantly higher mortality.46,53 ECCO₂R has been postulated to have two potential roles in ARDS. The first is control of hypercapnia using conventional lung-protective ventilation. The second is to facilitate ultra-protective ventilation (tidal volume < 4 mL/kg predicted body weight). The rationale behind the latter approach is that patients with severe ARDS have a smaller available lung volume, and that ventilation with tidal volumes of 6 mL/kg predicted body weight results in excessive lung strain.54 The addition of ECCO₂R to facilitate this “ultraprotective” approach has been shown to be feasible,35-37 although without demonstrable mortality benefit.

Acute exacerbations of COPD commonly require non-invasive ventilation (NIV)3 but 25%–50% of patients with COPD fail to improve and require invasive mechanical ventilation.55,56 These patients often have a prolonged hospital stay and an in-hospital mortality of 25%–39%.4-8,28 Given this, ECCO₂R is being considered as an adjunctive therapy to NIV to facilitate the withdrawal of NIV, avoid intubation or facilitate early extubation.28-30,57,58 A retrospective cohort study showed lower intubation rates and mortality than propensity-matched historical controls.32

Patients awaiting lung transplantation who develop life-threatening hypercapnia may also benefit from ECCO₂R as bridge to lung transplantation.59

**Modifications to respiratory management**

**Technical aspects**

There are some significant modifications to patient management associated with ECCO₂R. Cannulation has been associated with significant complications,31,36 although these may be reduced using venovenous rather than arteriovenous cannulation.29 The success and safety may also be improved by a structured approach using peri-procedural antibiotics, ultrasound, stiffer guidewires, tapered dilators and specific training.60 Bleeding complications associated with ECCO₂R are also common.26,61 Bleeding is partly due to the requirement for anticoagulation therapy, and partly due to the effects of centrifugal pumps and non-biological surfaces on the coagulation system, including acquired von Willebrand’s factor deficiency, reduction in platelet count and function and a reduction in coagulation factors.52-64 Unfortunately, bleeding and thrombosis co-exist with extracorporeal support both within the circuit and the patient, particularly with respect to deep vein thrombosis.65 Other conditions, including haemolysis related to the circuit and centrifugal pump, also occur.66

**ARDS**

Given the changes in native pulmonary physiology associated with ECCO₂R in ARDS, particularly the development of worsening atelectasis leading to hypoxaemia, PEEP needs to be re-titrated, potentially via a recruitment manoeuvre to maintain systemic oxygenation.37 Given that one of the goals of ECCO₂R is to reduce plateau pressures and tidal volumes, the net effect is to maintain mean airway pressure through an increase in PEEP and a reduction in driving pressure (the difference between plateau and PEEP).

**COPD**

As the work of breathing reduces with ECCO₂R, the key clinical goals are to facilitate either early extubation or to prevent intubation. ECCO₂R may also be used facilitate the removal of non-invasive ventilation,29 particularly in patients who tolerate NIV poorly.58 It is important to remember that the clinical progress will depend on the triggering aetiology and the ECCO₂R may be required for days to weeks.29,32 Thought should be given to the early institution of oral diet and mobilisation.

**Conclusions**

ECCO₂R is becoming a feasible means to facilitate ultra-protective mechanical ventilation or potentially avoid mechanical ventilation in select patient groups. While there is a clear theoretical rationale for ECCO₂R in COPD and purely hypercapnic respiratory failure, and to reduce the
mechanical power in ARDS, patient selection is crucial to the success of the technique. Consideration of the interaction between the mechanical and the natural lung, as well as the results of REST and SUPERNOVA will affect patient selection and clinical application of ECCO₂R in hypoxaemic respiratory failure. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of extracorporeal life support in the critically ill.⁶⁸-⁷¹

Competing interests
None declared.

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