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Extracorporeal carbon dioxide removal for lowering the risk of mechanical ventilation: Research questions and clinical potential for the future.

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Summary

As a result of technical improvements over recent years, extracorporeal carbon dioxide removal ($ECCO_2R$) now has the potential to play an important role in the management of adults with acute respiratory failure. There is growing interest in the use of $ECCO_2R$ for the management of both hypoxaemic and hypercapnic respiratory failure. However, there is limited evidence to support its use, and several questions remain about the best way to implement this therapy that can be associated with serious side effects. This position paper reflects the consensus opinion of an international group of clinician scientists with expertise in the management of acute respiratory failure and the use of $ECCO_2R$ therapies in these settings. Following a concise review of clinically relevant aspects of $ECCO_2R$, we provide a series of recommendations for clinical practice and future research, covering topics including the practicalities of $ECCO_2R$ delivery, indications for use and service delivery.

Key Messages (5 – 8 bullet points)

- Extracorporeal carbon dioxide removal is an emerging therapy for the treatment of acute respiratory failure.
- There is limited evidence to support the routine use of $ECCO_2R$, outside of clinical trials, in patients with acute respiratory failure.
- Future research should focus on veno-venous $ECCO_2R$.
- Further research is required to optimise the technology and identify if modifications can be made, especially to permit the use of less anticoagulation than is currently needed.
- $ECCO_2R$ may have a role in facilitating lower tidal volume ventilation than the current standard of care in patients with acute hypoxaemic respiratory failure, but further research is required to confirm this.
- In patients with acute hypercapnic respiratory failure, $ECCO_2R$ may be used to prevent endotracheal intubation, facilitate extubation, and act as an adjunct or alternative to non-invasive ventilation.
- Clinicians are encouraged to enroll patients into clinical trials investigating the use of $ECCO_2R$ in acute respiratory failure, and contribute to data registries.

Introduction and purpose of this paper

The use of extracorporeal carbon dioxide removal ($ECCO_2R$) for the management of acute respiratory failure in adults is rapidly gaining interest. However, there remains a limited evidence base to support its widespread use.[1–3] Many questions remain on how best to implement a therapy that may be associated with serious side effects.

This paper reflects the consensus opinion of an international group of clinician scientists with expertise in managing patients with acute respiratory failure and the use of various forms of extracorporeal life support in that setting. The aim of this position paper is to inform physicians, associated healthcare professionals, industry, and healthcare organisations about the potential role for $ECCO_2R$ in acute respiratory failure and identify where more research is required. Recommendations are provided for clinical practice (Table 1), future research (Table S1, supplementary appendix) and industry (Table S2).

Historical perspective

The concept of $ECCO_2R$ was initially proposed for three patients with refractory acute respiratory failure.[4] Avoiding barotrauma was the main concern during the early development of this experimental technique.[5,6] Subsequent use of $ECCO_2R$ focused on the most severe cases of hypoxaemic respiratory failure secondary to the acute respiratory distress syndrome (ARDS).[7] As understanding of the harmful effects of mechanical ventilation improved,[8,9] there was renewed interest in techniques that could facilitate more protective ventilation.[10]

What is $ECCO_2R$?

$ECCO_2R$ is a form of extracorporeal gas exchange that allows substantial carbon dioxide removal (>~20% of metabolic carbon dioxide production) from the blood at relatively low blood flow rates (~200 – 1500 ml/min). It usually has minimal effects on oxygenation. This contrasts with extracorporeal membrane oxygenation (ECMO) in which significantly higher blood flow rates (~2000 – 7000 ml/min) and an oxygen-rich sweep gas allow both efficient blood oxygenation and decarboxylation.[11] $ECCO_2R$ has previously been referred to as low-flow ECMO and also a form of respiratory dialysis.[12,13]

Carbon dioxide diffusion

Significant carbon dioxide removal occurs during $ECCO_2R$ at blood flow rates that are a fraction of those required for full-flow ECMO because blood decarboxylation is a more

efficient, non-limited process compared to oxygenation of blood. Carbon dioxide can be transported in solution, or bound to haemoglobin, or plasma proteins; however, the vast majority is carried within blood as bicarbonate.[14] Carbonic acid results when bicarbonate complexes with hydrogen ions, and this is disassociated into carbon dioxide and water by carbonic anhydrase. Unlike the relationship between oxygen and haemoglobin, the conversion of bicarbonate into free carbon dioxide occurs with linear kinetics and the process does not become saturated, therefore allowing carbon dioxide to diffuse more efficiently from blood. This means that lower blood flow rates are sufficient to achieve carbon dioxide removal than those necessary to provide systemic oxygenation during ECMO. Furthermore, because it has greater solubility, carbon dioxide diffuses across circuit membranes with greater efficiency than oxygen. $ECCO_2R$ therefore has minimal effects on oxygenation, and the "relatively low" blood flows requires the use of smaller cannulae than ECMO.

Rationale underlying the use of $ECCO_2R$

For patients with ARDS, mechanical ventilation using lower tidal volumes with limited plateau pressure is associated with reduced hospital mortality.[9,15] In addition, lower respiratory rates may also be protective.[16] These ventilation strategies reduce minute ventilation which may result in hypercapnia. Although hypercapnia is often well tolerated,[17] there are a number of important side effects.[18,19] Moreover, recent data have suggested an association between a partial pressure of carbon dioxide >6·7kPa (in the first 48-hours of ventilation) and increased mortality.[20] Using $ECCO_2R$ to prevent hypercapnia during the delivery of lower tidal volume ventilation underpins its use in patients with acute hypoxaemic respiratory failure.

As well, in non-intubated patients with hypercapnic respiratory failure, reduction of minute ventilation by using $ECCO_2R$ can reduce intrinsic positive end-expiratory pressure, reducing the oxygen cost of breathing.[21,22] These effects may all prevent the need for intubation. In intubated patients with hypercapnic respiratory failure, reduction of minute ventilation may allow earlier extubation.[23] Furthermore, $ECCO_2R$ may have a function as a temporary bridging therapy prior to lung transplant for patients with hypercapnia, during the pre-transplant period.

Practicalities of $ECCO_2R$

Vascular access

Vascular access is currently most often achieved through a veno-venous (VV) configuration, with the internal jugular or femoral veins the preferred access sites. $ECCO_2R$ can usually be

facilitated with a single, dual-lumen catheter, with lumen size dependent on the blood flow desired. The arterio-venous (AV) route has been used but the complications associated with AV-$ECCO_2R$, such as arterial vessel damage are potentially more impactful,[24] whilst the pumpless nature of these devices, entirely dependent on blood pressure, can lead to increased need for cardiovascular support. In many cases the catheter size and blood flow required for $ECCO_2R$ are much closer to those used in continuous renal replacement therapy and haemodialysis than those used for ECMO (Table 2).[25]

With present technology, we recommend that ultrasound-guided, aseptic placement of central catheters be used, regardless of the vascular access site, to reduce the risk of complications.[26,27] We also recommend considering VV-$ECCO_2R$ preferentially to AV-$ECCO_2R$ in most circumstances.

$ECCO_2R$ configuration

Similar to haemodialysis circuits, $ECCO_2R$ devices require circuit priming (usually <300 ml) prior to starting blood flow. In VV-$ECCO_2R$ circuits, blood flow is generated using a blood pump, with centrifugal and roller pumps being the most common.[14] Membrane lungs are designed with a mesh-like pattern, increasing the surface area for membrane lung-to-blood contact, and increasing gas exchange efficiency. The efficiency of each device (i.e. the quantity of carbon dioxide removed per minute adjusted to blood flow) should be an important consideration for clinicians since it determines the blood flow rate and hence the catheter size needed for adequate carbon dioxide removal. The properties of currently available devices are summarised in Table 2 but their respective efficiency is not well known. In patients receiving renal replacement therapy it has been demonstrated that there is no difference in catheter dysfunction or performance between jugular and femoral sites.[28] However for the delivery of $ECCO_2R$, the optimal insertion site and the impact of individual factors (e.g. obesity, abdominal hypertension) remain unknown.

Additional factors that may influence device efficiency in $ECCO_2R$ include recirculation. Described during ECMO, recirculation is a phenomenon where blood that is being returned to the systemic circulation is withdrawn back into the membrane lung by the drainage catheter.[29] Whilst the lower blood flow rates of $ECCO_2R$ may limit the impact of recirculation, it is possible that the use of smaller, dual-lumen catheters may increase the risk of recirculation. Recirculation could have impact on the delivery of $ECCO_2R$ in some subsets of patients.

Recommendations for future research

1. Measure the efficiency of $ECCO_2R$ devices through the quantification of carbon dioxide removed per minute and per 100ml of blood flow under standardized clinical conditions
2. Identify modifications that can be made to $ECCO_2R$ catheters to maximise blood flow whilst limiting complications.
3. Clarify if catheter insertion site and patient-specific factors that influence this (e.g. abdominal hypertension, patient body mass index) affect blood flow and complications.

Recommendations for industry

1. All devices should aim to integrate measurement of carbon dioxide removal and consider recirculation measurements to enable clinician titration of therapy.
2. Quantify how much carbon dioxide can be removed at different blood flows, as determined by different catheter sizes.
3. Integrate pressure measurements (e.g. drainage pressure, outlet pressure) in devices, to inform clinicians about early changes in device efficiency

Anticoagulation

Even though $ECCO_2R$ circuits are often heparin-bonded, systemic anticoagulation is required to prevent circuit thrombosis. Unfractionated heparin is typically administered to generate an activated partial thromboplastin time (aPTT) 1·5 – 2x normal although it is unknown whether this is optimal. All currently available devices require some degree of heparin to prevent thrombus formation. We recommend that suitability for systemic anticoagulation be one of the factors considered when assessing patients for $ECCO_2R$. Alternative treatment options should be sought in those patients deemed unsuitable for anticoagulation.

Recommendations for future research

1. Identify if the level of anticoagulation currently used in $ECCO_2R$ circuits can be significantly and safely reduced to limit haemorrhagic complications.
2. Investigate alternatives to heparin for anticoagulation in patients with contraindications (e.g. bleeding risks, heparin-induced thrombocytopenia).
3. Study the effects to the coagulation system during low blood-flow rates, with specific attention to the possible effects of shear stress. In addition, clarify if different levels of anticoagulation regimes are required at different blood-flow rates.

4. Investigate the safety and effectiveness of at least partial regional anticoagulation (e.g. citrate anticoagulation [30,31]), similar to renal replacement therapy

Emerging experimental techniques

Integrating a membrane lung into a continuous renal replacement circuit to deliver $ECCO_2R$ is an emerging technique. The blood pump and anticoagulation used for continuous renal replacement are sufficient to permit some degree of $ECCO_2R$. This setup remains experimental,[32–34] and further clinical trials are required.

Mechanisms to improve the effectiveness of $ECCO_2R$ have been investigated in pre-clinical studies using blood acidification (to increase carbon dioxide release) and respiratory electrodialysis combining a haemofilter, electrodialysis, and $ECCO_2R$.[35–38] Other experimental techniques include coating the membrane lung with carbonic anhydrase, the enzyme responsible for splitting carbonic acid into carbon dioxide and water. Pre-clinical studies suggest this technique can significantly augment carbon dioxide removal across membrane lungs.[39] These techniques remain experimental and should not be implemented without further research in humans.

Recommendations for future research

1. Clarify if experimental techniques to improve the efficiency of carbon dioxide removal can be safely delivered in humans receiving $ECCO_2R$, and whether they provide a clinically meaningful increase in $ECCO_2R$ efficiency in patients with acute respiratory failure.

Potential indications for $ECCO_2R$

We outline possible indications for $ECCO_2R$ below (Figure 1), but it is not possible currently to recommend which device should be used, nor the characteristics of a device required to achieve these.

Recommendations for industry

1. Adjust the design and characteristics of $ECCO_2R$ circuits to the indication for which it is being proposed.

Acute hypoxaemic respiratory failure

Enabling lower tidal volume ventilation

Use of a lung protective ventilation strategy is associated with reduced mortality in patients with ARDS and reduced pulmonary complications in patients without ARDS.[9,15,40,41] A recent global observational study of patients with acute hypoxaemic respiratory failure suggested that lung protective ventilation is not used in all indicated patients. The use of $ECCO_2R$ to achieve lung protective ventilation may improve ventilator tolerance, reduce the need for heavy sedation and neuromuscular blockade and overall facilitate its implementation.

Recommendation for future research

1. Study the feasibility and effectiveness of $ECCO_2R$ to facilitate lung protective ventilation in patients with acute hypoxaemic respiratory failure.
2. Clarify if the use of $ECCO_2R$ in acute hypoxaemic respiratory failure improves long-term outcomes and quality of life.

Facilitating lower than standard of care tidal volume ventilation

Mechanical ventilation using a tidal volume of 6 ml/kg predicted body weight (PBW) is regarded as best practice for patients with hypoxaemic respiratory failure meeting criteria for ARDS. It is possible that further reductions in tidal volume and plateau pressure may improve clinical outcomes in many patients.[13,42] A systematic review confirmed that although there was a consistent physiological effect in observational studies of $ECCO_2R$ in ARDS, the outcome data were variable.[1] A multi-centre randomized, controlled clinical trial of 79 patients with ARDS comparing a standard lung protective ventilation strategy (6ml/kg PBW) with tidal volumes of 3ml/kg PBW plus AV-$ECCO_2R$ did not demonstrate a difference in outcome between groups. However, a post-hoc subgroup analysis of patients with a ratio of partial pressure of arterial blood oxygen content to inspired fraction of oxygen (PaO_2/FiO_2 ratio) $\leq$20kPa suggested a benefit of the lower tidal volume strategy.[43] These findings suggest these patients may benefit from greater lung protection.[10,42]

There are several relevant ongoing clinical trials, which will potentially better inform clinicians. The REST trial (NCT02654327) is randomizing adult patients with acute hypoxaemic respiratory failure (PaO_2/FiO_2 ratio <20kPa) to either conventional lung-protective ventilation, or VV-$ECCO_2R$ plus lower tidal volume ventilation.[44] A European feasibility and safety study was completed in 2017, investigating the role of VV-$ECCO_2R$ in adult patients with at least moderate ARDS (SUPERNOVA, NCT02654327) with the aim of reducing tidal volumes to 4 ml/kg. Table 3 provides a list of trials which are either planned, in progress or completed but with results as yet unpublished.

There is insufficient evidence at present to inform clinicians about the role of $ECCO_2R$ in acute hypoxaemic respiratory failure. Currently, we do not recommend its routine use, and support the recommendations of the United Kingdom National Institute for Health and Care Excellence, and consensus guidelines from the French Intensive Care Society, that recommend patients receiving $ECCO_2R$ should do so as part of a clinical trial.[45,46]

Recommendations for future research

1. Evaluate if using $ECCO_2R$ to enable mechanical ventilation with lower than current standard of care tidal volumes, improves outcomes in patients with moderate to severe acute hypoxaemic respiratory failure.
2. Investigate which subsets of patients with acute hypoxaemic respiratory failure may benefit from lower than standard of care tidal volume ventilation facilitated by $ECCO_2R$.

Acute hypercapnic respiratory failure

Chronic Obstructive Pulmonary Disease (COPD)

Acute hypercapnic respiratory failure in patients with COPD, is another potential indication for $ECCO_2R$. Although non-invasive ventilation is very effective in these patients, 5-20% require intubation,[47,48] and these patients have an in-hospital mortality of approximately 30%.[48]

A systematic review of case series' and case-control studies demonstrated that non-invasive ventilation with adjunctive $ECCO_2R$ therapy prevented intubation in 93% of patients with COPD.[2] In addition, preliminary, retrospective data suggest there may be economic benefit in using $ECCO_2R$ to avoid invasive mechanical ventilation, because it reduces intensive care unit and hospital length of stay.[49]

The use of $ECCO_2R$ for facilitating extubation from invasive mechanical ventilation in hypercapnic COPD patients is another potential indication. In an elegant physiological demonstration, $ECCO_2R$ reduced respiratory muscle work and carbon dioxide production in intubated patients during weaning.[50] Two pilot studies have demonstrated it is feasible to use $ECCO_2R$ to facilitate extubation in patients with COPD.[23,51] Further data is necessary before this approach could be considered standard of care for these patients. A list of planned, or in progress, clinical trials is provided in Table 4. It is possible that using $ECCO_2R$ to facilitate extubation may also have a role in acute hypoxaemic respiratory failure.

Recommendations for future research

1. Undertake clinical trials to study the role of $ECCO_2R$ in acute hypercapnic respiratory failure (such as COPD exacerbation), including:
    a. Identify if it can be safely and effectively used in combination with non-invasive ventilation to prevent the requirement for invasive mechanical ventilation. Furthermore, identify factors (e.g. clinical and physiological factors) which may predict the failure of $ECCO_2R$ in preventing invasive mechanical ventilation.
    b. Establish if $ECCO_2R$ can facilitate extubation from invasive mechanical ventilation.
    c. Clarify if the use of $ECCO_2R$ in acute hypercapnic respiratory failure has a mortality benefit, improves long-term functional recovery and quality of life as an adjunct in both invasive and non-invasive ventilation.

<u>Asthma</u>

Severe life-threatening asthma is characterized by bronchospasm, airflow obstruction and hypercapnia. In a very selected patient group who are refractory to conventional asthma management, the provision of $ECCO_2R$ could potentially mitigate severe life-threatening exacerbations by minimizing dynamic hyperinflation and intrinsic positive end expiratory pressure. The current body of literature in this area however is limited to case reports of asthmatics already receiving invasive mechanical ventilation and subsequently assisted with $ECCO_2R$.[52–55]

Recommendations for future research

1. Establish whether $ECCO_2R$ can prevent the requirement for invasive mechanical ventilation, and whether this is associated with improved clinical outcomes, in status asthmaticus. However, undertaking studies within this population may be challenging.
2. Study the role $ECCO_2R$ may have to facilitate extubation from invasive mechanical ventilation and whether this is associated with improved clinical outcomes in severe status asthmaticus.

<u>Bridge to Lung Transplantation</u>

There is a strong rationale for considering $ECCO_2R$ as a bridge to lung transplantation in patients with decompensated respiratory failure, but data supporting its use in these patients is limited. A retrospective analysis of 20 patients bridged with $ECCO_2R$ whilst awaiting lung transplant demonstrated an improvement in hypercapnia and acidosis within the first twelve hours of application. After a bridging period ranging from four to eleven days, 19 patients

(95%) were successfully transplanted, and hospital survival was 75%.[56] In a cohort of 72 patients awaiting lung transplantation in whom extracorporeal support was used, 70% of patients participated in daily physical activity, significantly higher rates of ambulation were observed compared to unsupported patents, and two year survival was 84%.[57]

Recommendations for future research

1. Identify if $ECCO_2R$ can be used as bridge to lung transplantation.

Complications associated with $ECCO_2R$

$ECCO_2R$ may be associated with a range of complications and we provide a summary of these in Table 5.

Catheter-specific

The risk of complications related to catheter insertion differ significantly between arterial and venous insertion sites, but complications from both include bleeding, infection and catheter dislodgement. Arterial catheterisation is associated with more risk, and complications include distal limb ischaemia, compartment syndrome and pseudo-aneurysm formation. This risk may be mitigated by using smaller calibre catheters. As technology develops there is hope that catheter size will be reduced further, leading to the incidence of catheter-related complications that will approach that of central venous catheters.[58] Although safety data from the Xtravent study are reassuring (three patients experienced catheter-specific complications),[43] the increased risk associated with AV-$ECCO_2R$ contribute to our recommendation that it should be avoided beyond centres already familiar with this technology.

Bleeding risk

Despite the use of heparin-bonded circuits, patients receiving $ECCO_2R$ usually require low-level. It is unclear whether haemorrhagic complications are more common with ECMO or with $ECCO_2R$, however the evidence base for this is limited. In a recent clinical trial comparing ECMO to conventional care for the treatment of severe ARDS, there was no difference between groups in the rates of massive bleeding or haemorrhagic stroke, although patients receiving ECMO did experience more episodes of bleeding that necessitated blood transfusion.[59] An observational study of patients receiving ECMO for severe respiratory failure demonstrated that most patients had intracranial haemorrhage at admission to ICU, suggesting that the risk of intracranial haemorrhage is associated with illness severity rather than the application of ECMO.[60]

In studies of $ECCO_2R$ to-date, the rate of significant haemorrhagic complications range between 2 – 50%.[1,2] In a recent pilot study of VV-$ECCO_2R$, there were bleeding complications necessitating blood transfusion in 40% of patients, although none were deemed significant and no patient experienced haemodynamic compromise.[61] However, in one older study all twenty-one patients who received VV-$ECCO_2R$ experienced haemorrhagic complications, and it was necessary to discontinue therapy in seven patients.[7] In a small observational study of patients treated with the Hemolung Respiratory Assist System, four of seven patients had clinically relevant bleeding. Thrombocytopenia, factor XII deficiency and acquired von-Willebrand syndrome were identified during therapy, with spontaneous recovery after $ECCO_2R$ was discontinued.[62] Currently, we strongly recommend regular monitoring of coagulation indices in all patients receiving $ECCO_2R$, with cessation of therapy when there is significant bleeding.

Haemolysis

Modern $ECCO_2R$ pumps and circuits are designed to limit the shear force applied to blood as it passes through the pump. However there remains a significant risk of haemolysis and clot formation, and this risk may be greater at lower blood-flow rates. It is recommended that in patients with decreasing haemoglobin, screening for haemolysis occurs (e.g. free haemoglobin, lactate dehydrogenase) as part of clinically relevant investigations for an underlying cause. Haemolysis is known to be associated with acute kidney injury (AKI),[63] however it is unknown if the degree of haemolysis induced by $ECCO_2R$ is associated with AKI, or the frequency of AKI, in this setting. The ongoing need for $ECCO_2R$ should be reviewed in all patients with circuit-induced haemolysis.

Recommendations for future research

1. Clarify the risks (e.g. vascular complications, haematological) associated with modern $ECCO_2R$ devices, particularly in VV-circuits. This should be considered a research priority.
2. Identify if there is a risk of haemolysis-induced renal function during $ECCO_2R$ therapy.

Ongoing and future clinical trials utilising modern $ECCO_2R$ devices will better inform clinicians about the risks associated with this technology (Tables 3 and 4).

Resources / infrastructure for $ECCO_2R$

Who and what is needed to deliver $ECCO_2R$?

A team of highly motivated and trained physicians, registered nurses, respiratory therapists and physiotherapists is required for the safe and effective delivery of $ECCO_2R$. Similar to the recommendations for ECMO,[64] every member of staff treating patients receiving $ECCO_2R$ should have received $ECCO_2R$-specific training, and demonstrate ongoing competencies. We also recommend that an attending physician with experience in managing patients on $ECCO_2R$ should be available to provide 24-hour coverage. Team members will require ultrasonographic vascular access skills for percutaneous cannulation. Importantly, and unlike ECMO, a dedicated perfusionist is typically not required to manage the $ECCO_2R$ circuit, but may be an important part of the team in some centres.

As it is still mainly a research tool, at present $ECCO_2R$ should be delivered within the setting of a clinical trial. Each centre should have the necessary expertise to manage the $ECCO_2R$ device, and its complications. This is in contrast to the recommendations for delivering ECMO, where therapy delivered in expert centres may be associated with improved safety and outcomes.[64–67] We recommend those using $ECCO_2R$ should be proficient in the delivery of continuous renal replacement therapies.

Training requirements for implementing $ECCO_2R$ within a critical care environment

It is anticipated that much like renal replacement therapy, the provision of $ECCO_2R$ for acute respiratory failure will be met by critical care units. Staff require appropriate training to manage the patient, the device, and to recognize relevant complications. For example in the REST trial training was delivered by a team of experienced clinicians and support staff.[44] Delivering training in batches allowed units to establish a core set of staff who were skilled in the management of patients receiving $ECCO_2R$. We recommend that a specific training programme delivered by staff experienced in managing patients receiving $ECCO_2R$ for acute respiratory failure should occur within each unit delivering $ECCO_2R$. The training programme should be at least as extensive as that delivered for renal replacement therapy, and should include device-specific training and associated complications. After establishing an $ECCO_2R$ service, staff competency should be regularly assessed.

Program evaluation and quality assurance

Delivering a safe and effective service is of paramount importance. Should $ECCO_2R$ become routine in the management of acute respiratory failure, there will need to be robust evaluation and quality assurance programmes. We support the recommendations from a previous position paper for the organisation of ECMO services and believe similar processes should be considered for regular review of $ECCO_2R$ services.[64] In brief, evaluation programmes should include regular review of outcomes for patients receiving $ECCO_2R$,

prompt review of any significant adverse event associated with $ECCO_2R$, and regional/national unit accreditation. These should take place in addition to each unit's local evaluation and quality assurance programmes. Sites using $ECCO_2R$ as part of clinical care should be strongly encouraged to input data into a registry (e.g. Extracorporeal Life Support Organisation www.elso.org) to facilitate quality assurance.

Recommendations for future research:

1. Establish appropriate outcome measures to evaluate the safety of an $ECCO_2R$ service

Summary of recommendations and research questions

$ECCO_2R$ is a novel and attractive technique for the management of respiratory failure but there is a paucity of evidence to support its routine application. In keeping with recommendations from the United Kingdom National Institute for Health and Care Excellence and consensus guidelines from the French Intensive Care Society, which encourage clinicians to enrol patients into ongoing clinical trials and to collaborate in data collection initiatives (e.g. the Extracorporeal Life Support Organization registry),[45,46] we believe the use of $ECCO_2R$ in the clinical setting should be primarily confined within research protocols**.** Organisations such as the International ECMO Network (ECMONet; www.internationalecmonetwork.org) can help to conduct the necessary studies and to coordinate collaboration in this arena.

Search strategy and selection criteria

The authors searched PubMed for the terms "acute respiratory failure" [All Fields] AND / OR "extra-corporeal carbon dioxide removal" [All Fields], "renal replacement therapy" [All Fields} and "haemolysis" [All Fields] with no restriction on language or date. This search was performed on 10th December 2017, and updated on 10th June 2018. References were also searched from within existing systematic reviews.

Table 1: Summary of recommendations for clinical practice

	Recommendations
Practicalities of $ECCO_2R$ (Vascular access, circuit configuration, anticoagulation, emerging experimental techniques)	• Use ultrasound-guided, aseptic central catheter placement • Consider VV-$ECCO_2R$ over AV-$ECCO_2R$ • AV-ECCO2R should be avoided beyond centres already familiar with this technology • Alternative treatment options should be sought for patients deemed unsuitable to receive anticoagulation. • We strongly recommend regular monitoring of indices of coagulation in all patients receiving $ECCO_2R$ • Cease therapy where there is a concern regarding significant bleeding
Acute hypoxaemic respiratory failure	• There is insufficient evidence to recommend the routine use of $ECCO_2R$ in patients with acute hypoxaemic respiratory failure
Acute hypercapnic respiratory failure	• Further data is necessary before $ECCO_2R$ use could be considered standard of care
Clinical trial / registry enrolment	• Clinicians are strongly encouraged to recruit eligible patients to clinical trials of $ECCO_2R$, or contribute data from non-trial patients receiving $ECCO_2R$ to international registries (e.g. ELSO)
Service delivery	• Centres using $ECCO_2R$ should be proficient in the delivery of continuous renal replacement therapies • An attending physician with experience of $ECCO_2R$ should be available to provide 24-hour coverage • A specific training programme, delivered by staff experienced in managing patients receiving $ECCO_2R$ for acute respiratory failure, should occur within each unit delivering an $ECCO_2R$ service
Program evaluation	• Providers of $ECCO_2R$ services should regularly review outcomes of all patients receiving therapy, with prompt review of any associated significant adverse event.

Table 2: Examples of available $ECCO_2R$ devices

Company	Device	Flow Rates (ml/min)	Catheter Size (Fr) *	Preferred Insertion Site *	Membrane Size (m^2)	Potential Indications
ALung	Hemolung Respiratory Assist System	350 – 550	15· 5	Femoral, internal jugular	0·59	1. Hypercapnic respiratory failure refractory to NIV 2. Facilitate lung protective ventilation during IMV
Novalung / Fresenius	AV-iLA[a]	100 – 1500	13 – 17	Femoral	1·3	1. Lower tidal volume ventilation in ARDs 2. Weaning from IMV 3. COPD exacerbations 4. Bridge to lung transplant [b] 5. Bronchopleural fistula
Novalung / Fresenius	iLA miniLung petite kit	100 – 800	18	Internal jugular	0·32	1. Lower tidal volume ventilation in ARDS 2. Weaning from IMV 3. Avoid intubation 4. Bridge to lung transplant
Novalung / Fresenius	iLA / Novalung miniLung kit [c]	350 – 2400 [d]	18 – 24	Femoral, internal jugular	0.65	1. Lower tidal volume ventilation in ARDS 2. Weaning from IMV 3. Avoid intubation 4. Bridge to lung transplant
Novalung / Fresenius	iLA activve	500 – 4500	13 – 24	Femoral, internal jugular	1·3	1. Lower tidal volume ventilation in ARDS 2. Weaning from IMV 3. Avoid intubation 4. Bridge to lung transplant

ESTOR	ProLUNG	<450	13·5	Femoral, internal jugular	1·8	1. Moderate ARDS 2. COPD exacerbations: Prevent IMV, facilitate weaning 3. Bridge to and post lung transplant 4. Bronchopleural fistula or other airway lesions
Baxter	PrismaLung [e]	<450	13 – 14	Internal jugular	0·32	1. Physician discretion
BBraun	Diapact	200 – 500	13	Femoral, internal jugular	1·35 – 1·8	1. Moderate ARDS 2. COPD exacerbations: Prevent IMV, facilitate weaning 3. Bridge to and post lung transplant 4. Bronchopleural fistula or other airway lesions

IMV: Invasive mechanical ventilation; NIV: Non-invasive ventilation; COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome.

* Catheter size and insertion site may depend on individual patient factors.

a. Pumpless system.

b. This device has been used in a pulmonary artery – left atrium configuration as a bridge to lung transplant in patients with pulmonary hypertension.

c. iLA miniLung and Novalung miniLung are two different devices that share similar characteristics.

d. Flow rates of 1200 – 2400ml require 3/8 connector size.

e. This device is used in conjunction with the Prismaflex® control unit during continuous renal replacement therapy or haemopurification.

Table 3: Ongoing, planned or unpublished clinical trials investigating acute hypoxaemic respiratory failure

Trial Name	Registration details	Population	Enrolment	1. Intervention 2. Target	Comparator	Primary outcome	Status
pRotective vEntilation with veno-venouS lung assisT in respiratory failure (The REST Study)	NCT02654327 ISRCTN31262122	Mechanically ventilated adult patients within 48 hours of acute hypoxaemic respiratory failure (PaO_2/FiO_2 ratio < 20kPa) receiving at least PEEP of 5	1120	1. VV-$ECCO_2R$ 2. Vt ≤ 3ml/kg PBW and a Pplat ≤ 25cmH_20, maintaining the arterial pH ≥ 7.20	Standard ventilation (Vt 6ml / kg PBW)	90-day mortality	Recruiting
Ultra-protective Pulmonary Ventilation Supported by Low Flow $ECCO_2R$ for Severe ARDS (U-Protect)	NCT02252094	Mechanically ventilated adults with at least moderate ARDS, reversible disease, expected to be ventilated for >48 hours.	50	1. VV-$ECCO_2R$ (as part of a renal replacement device) 2. Ultra-protective ventilation (Vt ≤3ml/kg PBW) with Pplat ≤25 cmH_2O	Standard ventilation (6ml/kg PBW)	Ability to achieve Pplat <25cmH_2O	Recruiting
Strategy of UltraProtective lung ventilation with Extracorporeal CO_2 Removal for New-Onset moderate to	NCT02282657	Mechanically ventilated adults with an expected ventilation duration >24 hours, whom have moderate ARDS (PaO_2/FiO_2 ratio 13·33 -	Pilot study: 95	1. 2-hour run in period followed by AV- or VV-$ECCO_2R$ 2. Reduction in tidal volume (± respiratory rate) maintaining Pplat 23 – 25, and $PaCO_2$	Nil	Vt reduction to 4 mL/kg, maintaining pH and $PaCO_2$ to ± 20% of baseline.	Completed but unpublished

seVere ARDS (SUPERNOVA)		26·67kPa)		at baseline (±20%)			
Low-Flow CO_2 Removal for Mild to Moderate ARDS With PRISMALUNG	NCT02606240	Mechanically ventilated adults with mild to moderate ARDS, expected to be mechanically ventilated for >24 hours.	20	1. VV-ECCO$_2$R (as part of a renal replacement) 2. Ultra-protective ventilation (Vt 4ml/kg PBW, Pplat 23-5 cmH_2O)	Nil	Number of participants who achieve a Vt of 4 ml/kg while maintaining pH and $PaCO_2$ to ± 20% of baseline values obtained at Vt of 6ml/kg.	Completed but unpublished
"Low Flow" CO_2 Removal on RRT (Prismalung)	NCT02590575	Mechanically ventilated adults, expected to be ventilated for >24 hours, with a $PaCO_2$ ≥55mmHg, plateau pressure >25cmH_2O, and pH <7·30, who require renal replacement therapy.	20	1. VV-ECCO$_2$R (as part of a renal replacement device) 2. Reduction of Vt and Pplat to achieve the baseline $PaCO_2$.	Nil	Changes in $PaCO_2$, acid-base status, Vt and Pplat	Completed but unpublished
Correction by ECCO2-R of Hypercapnia in Patients With DVP in	NCT03303807	Moderate-severe ARDS with pulmonary vascular dysfunction on	20	1. VV-ECCO$_2$R (as part of a renal replacement device) 2. Correction of hypercapnia under	Nil	Percentage of patients with corrected hypercapnia (defined as 20%	Not yet recruiting

Moderate to Severe ARDS Under Protective Ventilation. (COVAP)		echocardiography and refractory hypercapnia ($PaCO_2 \geq 6{\cdot}4kPa$)		protective ventilation (tidal volume 6ml/kg (PBW), plateau pressure $\leq 30cmH_2O$)		decrease in $PaCO_2$ two hours after initiation of $ECCO_2R$)	

PEEP: Positive end-expiratory pressure; VV-$ECCO_2R$: veno-venous extracorporeal carbon dioxide removal; PBW: Predicted body weight; Vt: Tidal volume; Pplat: plateau pressure; ARDS: Acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; DVP: Pulmonary vascular dysfuncton.

Table 4: Ongoing or planned clinical trials investigating acute hypercapnic respiratory failure

Trial Name	Registration details	Population	Enrolment	Intervention	Comparator	Primary outcome	Status
$ECCO_2R$ as an Adjunct to NIV in AECOPD	NCT02086084	Adults with acute exacerbation of COPD, with persistent arterial pH <7.30 primarily due to hypercapnic respiratory failure after standard therapy and at least 1 hour of NIV	24	VV-$ECCO_2R$ + NIV	NIV alone	Time to cessation of NIV (≥6 hours without NIV)	Recruiting
Weaning Form Mechanical Ventilation Using Extracorporeal CO_2 Removal (WeanPRO)	NCT02259335	Mechanically ventilated adults who meet readiness criteria for weaning and fail a T-piece trial after 1 hour or before for a rise in $PaCO_2$ >20% from baseline and with f/Vt ratio >100	Pilot study: 15	VV-$ECCO_2R$ during the T-piece trial	Nil	Passing a weaning trial using a T-piece method, and avoiding reintubation within 48-hours of $ECCO_2R$ device removal	Recruiting
Extracorporeal CO_2 Removal With the Hemolung RAS for Mechanical Ventilation Avoidance During Acute Exacerbation of COPD (VENT-AVOID)	NCT03255057	Adults with acute exacerbation of COPD and hypercapnic respiratory failure with <4 days of non-invasive ventilation or invasive ventilation for <4 days	300 – 800 (adaptive design)	VV-$ECCO_2R$ as an adjunct or alternative to standard-of-care invasive mechanical ventilation	Standard of care non-invasive or invasive mechanical ventilation alone	Ventilator free days at day 60 from randomisation	Recruiting

VV-$ECCO_2R$: Veno-venous extracorporeal carbon dioxide removal; NIV: Non-invasive ventilation; COPD: Chronic obstructive pulmonary disease; $PaCO_2$: Partial pressure of arterial carbon dioxide; f/Vt: rapid shallow breathing index.

Table 5: Complications associated with $ECCO_2R$

Catheter insertion	Catheter-site bleeding
	Catheter-site infection
	Inadvertent arterial insertion (in VV-$ECCO_2R$)
	Catheter dislodgement or kinking of tubing
	Haematoma, aneurysm or pseudo-aneurysm formation
	Compartment syndrome
	Distal limb ischaemia (in AV-$ECCO_2R$)
Therapy	Worsening hypoxaemia during lower tidal volume ventilation
	Bleeding (related to anticoagulation)
	Haemolysis
	Heparin-induced thrombocytopenia
	Acquired coagulopathy (e.g. acquired von-Willebrand syndrome)
	Air embolism
	Recirculation
Device failure	Pump failure
	Oxygenator failure
	Heat exchanger malfunction
	Clot formation
	Air within circuit

Figure 1: Potential indications for $ECCO_2R$

$ECCO_2R$ is an emerging therapy that may have benefit in facilitating lower tidal volume ventilation, preventing intubation, facilitating extubation, and as a bridging therapy to lung transplant.

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List of abbreviations

$ECCO_2R$: Extracorporeal carbon dioxide removal

ARDS: Acute respiratory distress syndrome

ECMO: Extracorporeal membrane oxygenation

VV: Veno-venous

AV: Arterio-venous

aPTT: activated partial thromboplastin time

PBW: Predicted body weight

PaO2/FiO2 ratio: Ratio of partial pressure of arterial blood oxygen content to inspired fraction of oxygen

COPD: Chronic obstructive pulmonary disease

AKI: Acute kidney injury

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