Extracorporeal membrane oxygenation for adults with respiratory failure secondary to cardiorespiratory disease: evolving indications and clinical practice

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Shareable abstract (@ERSpublications)
Extracorporeal membrane oxygenation (ECMO) can provide support for carefully selected patients with reversible cardiorespiratory disease or can be used as a bridge to transplant. Advances in technology and service delivery will improve patient outcomes. https://bit.ly/3AOikYu

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Abstract

Extracorporeal membrane oxygenation (ECMO) can support patients with severe cardiorespiratory failure presenting with hypoxia who would otherwise have not survived. Patient selection for ECMO is challenging and relies on the integration of physiological variables with an assessment of reversibility of the underlying condition or suitability for transplantation. In this review, we focus on patients with cardiorespiratory disease who may present with severe hypoxia. We will discuss the indications and contraindications for ECMO; the evidence for ECMO, which is limited to a small number of clinical trials and registry data; the complications of ECMO; expanding technologies and indications; the development of a multidisciplinary ECMO network; and future research. The aim is to increase knowledge of this important area for respiratory physicians.

Educational aims

- To understand the indications, contraindications and complications of extracorporeal membrane oxygenation (ECMO) as applied to cardiorespiratory disease in patients presenting with hypoxaemic respiratory failure.
- To gain knowledge of the evidence base for the use of ECMO in patients with cardiorespiratory disease including the patients most likely to benefit from this technology.
- To be aware of the expanding technology and indications for ECMO in patients with cardiorespiratory disease.

Introduction and history

Severe cardiorespiratory failure significantly contributes to mortality and morbidity in acute care settings. It results from a variety of diseases or injuries some of which are listed in table 1. The physiological interaction between the cardiac and respiratory systems requires co-management in all of these cases. In patients suffering from profound and life-threatening cardiorespiratory failure, conventional mechanical ventilation and pharmacological support may be insufficient to sustain the patient's life. In such instances, extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS), where blood is removed from the circulation, oxygenated and pumped back into the body, offers an advanced life-support strategy as a bridge to decision, optimising and continuing treatment, recovery, and organ transplantation or durable support (for end-stage heart failure).

The first documented proposal to oxygenate blood outside the body and return it to the circulation was made by Robert Hooke in 1667. Nearly 250 years later, and just under 40 years after the discovery of heparin in 1916, the first heart lung machine was used in humans in 1953 [4].

TABLE 1 Diseases and injuries that can cause severe cardiorespiratory failure that may require support with veno-venous, veno-arterial or hybrid extracorporeal membrane oxygenation in adults [1–3]

Acute respiratory distress syndrome (*e.g.* viral/bacterial pneumonia and aspiration)
Acute eosinophilic pneumonia
Diffuse alveolar haemorrhage or pulmonary haemorrhage
Severe asthma
Thoracic trauma (*e.g.* traumatic lung injury and severe pulmonary contusion)
Severe inhalational injury
Large bronchopleural fistula
Peri-lung transplant (*e.g.* primary lung graft dysfunction and bridge to transplant)
Pulmonary embolus
Ischaemic heart disease
Dilated cardiomyopathy
Intractable arrhythmias
Septic cardiomyopathy
Viral myocarditis

Longer term support was first reported in 1972 after the development of the membrane oxygenator pioneered by Robert Bartlett and still in use today [5]. While paediatric ECMO became the standard of care in the 1980s [5], outcomes of ECMO for adult cardiorespiratory disease were disappointing. The use of ECMO for adults was therefore confined to enthusiasts in specialist centres and was overseen by the Extracorporeal Life Support Organization (ELSO), formed in 1989 to study and improve the outcomes for patients supported on ECMO [5]. 20 years later with the onset of the H1N1 influenza pandemic the use of ECMO expanded rapidly and was shown when combined with techniques in the advanced management of respiratory failure to be a lifesaving support mechanism [6], the use of which expanded again rapidly during the recent COVID-19 pandemic.

The ECMO circuit

ECMO is applied in specialist critical care settings, for patients with severe respiratory and cardiac failure, and for whom conventional management strategies have failed. ECMO functions by removing a large volume of blood (3–5 L) from the patient *via* large cannulae, pumping it through an artificial lung or membrane oxygenator consisting of a dense mesh of hollow gas-filled fibres, where carbon dioxide is removed and oxygen is added, and returning it through another large cannula. This allows the critically unwell patient's organs to remain oxygenated for some time, while the underlying cardiorespiratory pathology resolves [1].

There are two main forms of ECMO support, which are selected based on the clinical scenario and which have been extensively reviewed elsewhere [7–9].

1) Veno-venous (VV)-ECMO
   - Oxygenated blood is returned *via* a cannula to the inferior and/or superior vena cava (VV), or to the pulmonary artery (V-PA).
   - VV-ECMO is primarily indicated in severe respiratory failure and relies on the patient's own cardiac function to deliver oxygenated blood to the body. V-PA configurations also provide right ventricular assist.
2) Peripheral and central veno-arterial (VA)-ECMO
   - Peripheral VA-ECMO drains blood from the vena cava and returns oxygenated blood to the patient's descending aorta *via* an arterial cannula in a large artery, causing retrograde flow up the aorta. Central VA-ECMO returns the blood to the ascending aorta and is more physiological and mainly used post-cardiac surgery. The application of VA-ECMO during refractory cardiac arrest is known as extracorporeal cardiopulmonary resuscitation (ECPR).
   - VA-ECMO is primarily indicated in cardiogenic shock states when the myocardium benefits from a period of rest, whilst oxygenated blood flow is continuously delivered to the arterial system.

VV- and VA-ECMO can be combined, adapted, and at times benefit from adjunct support devices [7–9]. This review will focus on ECMO for respiratory and cardiorespiratory failure concentrating on diseases presenting with hypoxia.

Physiological indications for ECMO

The ELSO produce regular guidance on the use of ECMO. The current ELSO guidelines state that "VV-ECMO should be considered in patients with severe reversible respiratory failure that is refractory to optimal medical management or in patients as a bridge to lung transplant or those suffering primary graft dysfunction after lung transplant" [2]. VA-ECMO in cardiorespiratory disease is indicated for patients with combined respiratory and cardiac failure where there is evidence of a low cardiac output state as well as critical hypoxia that is likely to be reversible [3]. As a guide as to when to initiate ECMO in these patients, ELSO currently recommends considering ECMO when the patient's predicted mortality with conventional management approaches 50% [1]. Delivery of adequate amounts of oxygen to the tissues is dependent on numerous factors including adequate saturation of haemoglobin, amounts of haemoglobin and cardiac output. Defining those patients with critical tissue hypoxia, who are at high risk of death and might benefit from ECMO is challenging. There is no one measure or factor that reliably predicts ECMO requirement and therefore this assessment needs an integrated bedside approach [10].

The rationale for the use of VV-ECMO in respiratory failure is two-fold. First, it can provide gas exchange through adequate oxygenation and carbon dioxide removal when the native lung cannot perform this task. Secondly, when combined with "lung rest" it can prevent ventilator-associated lung injury by avoiding overventilation [2].

The severity of respiratory failure can be defined by the partial pressure of oxygen to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}) ratio with severe disease classified as a P_{aO_2}/F_{IO_2} ratio of <100 mmHg. Patients in this category have a mortality of over 45% with conventional treatment [11]. The current standard indication for consideration of VV-ECMO for hypoxaemic respiratory failure is a P_{aO_2}/F_{IO_2} ratio of <80 mmHg based on these data and the inclusion criteria from the EOLIA trial [12]. Other criteria for the use of ECMO include a Murray score of $\geqslant$3, which combines P_{aO_2}/F_{IO_2} ratio, positive end-expiratory pressure (PEEP), lung compliance and chest radiography findings to delineate a severity score for acute respiratory distress syndrome (ARDS) and was used in the CESAR trial [6].

Permissive hypercapnia resulting in a moderate reduction in pH has become the standard of care in severe acute respiratory failure [13]. Having said this, severely raised levels of carbon dioxide are still associated with a significantly increased mortality even in the post ARDSNET era. The ELSO guidelines currently recommend that patients with pH of <7.25 despite optimal management should be considered for support with VV-ECMO [2], again in keeping with the inclusion criteria from the EOLIA trial [12]. This is particularly important for patients where an extremely low pH is associated with cardiovascular collapse [14].

One of the main mechanisms by which VV-ECMO may confer an advantage to patients with severe acute respiratory failure is the avoidance of ventilator-induced lung injury (VILI) [15]. VILI is the result of barotrauma, volutrauma, atelectotrauma and biotrauma that occurs when positive pressure ventilation is applied to the lung. VILI can be reduced by using low or ultra-low tidal volumes, optimal PEEP and plateau pressures, reductions in respiratory rate and the minimisation of mechanical power. This "lung rest" can also, in some cases, have profound effects on the heart by reducing pulmonary vascular resistance and improving right ventricular pre-load leading to improved haemodynamics [16].

In patients with combined cardiac and respiratory failure VA-ECMO or a hybrid combination of VV- and VA-ECMO may be required. This can improve tissue delivery of oxygen through both oxygenation and augmented blood flow [3, 17]. Indications for VA- or hybrid ECMO in this circumstance include evidence of low cardiac output with a systolic blood pressure of <90 mmHg and end-organ hypoperfusion evidenced by a high lactate, a low urine output or low consciousness level [3]. In this state, when VV-ECMO alone is unlikely to adequately support the patient with combined cardiorespiratory instability, VA- or hybrid ECMO can be considered [3, 17].

Due to the risks and costs of ECMO, current guidelines and expert consensus states that all standard treatments should be exhausted before its initiation [18, 19]. This management should be instituted early to avoid delaying the initiation of ECMO, which could be detrimental to outcomes [2].

Contraindications to ECMO

ECMO support does not benefit everyone and must be reserved for the sickest patients with the lowest risk of complications and those who have a reversible condition, limited comorbidities and excellent rehabilitation potential. However, the only absolute contraindication to ECMO is anticipated non-recovery to decannulation. This would include patients with end-stage comorbidities which would place a

TABLE 2 Relative contraindications for veno-venous extracorporeal membrane oxygenation (ECMO) or veno-arterial or hybrid ECMO for adult cardiorespiratory disease [2, 3, 17]

Older age (increasing risk of death with increasing age, no threshold is established)
Mechanical ventilation for more than 7 days with P_{plat} >30 cmH_2O and F_{IO_2} >90%
Contraindications to anticoagulation, including:
Central nervous system haemorrhage
Any other system uncontrollable haemorrhage
Immunosuppression
Inability to rehabilitate post-ECMO, including:
Irreversible and incapacitating central nervous system pathology
End-stage and significantly life-limiting comorbidities
Vascular disease prohibiting cannulation

P_{plat}: plateau pressure; F_{IO_2}: fraction of inspired oxygen.

significant limitation on their life expectancy with or without ECMO support (*e.g.* end-stage malignancy) [2]. Other relative contraindications to ECMO are listed in table 2 and need to be assessed on a case-by-case basis. Most relate to the challenge of anticoagulation.

While there is no specific age cut-off at which ECMO no longer confers benefit, increasing age is associated with an increasing risk of death with the odds ratio of death during hospitalisation being double for those patients in their sixties when compared to those who are under 40 years of age [20, 21]. Duration of mechanical ventilation of more than 7 days at high oxygen and ventilatory settings is also a relative contraindication to ECMO. Further studies are required to update this important area, as the cut-off of 7 days has been brought into question [22].

Scoring systems for ECMO survival

There are a number of scoring systems that have been developed to help predict survival of patients on ECMO. The most widely established of these are the respiratory ECMO survival prediction (RESP) score for VV-ECMO and the survival after VA-ECMO (SAVE) score for VA-ECMO both developed by Schmidt and co-workers [23, 24]. Both scores take into account a number of factors independently associated with outcomes once the patient is established on ECMO. These scores include age, diagnosis, duration of mechanical ventilation and presence of other comorbidities and organ failures [23, 24].

Evidence for ECMO in specific conditions

The evidence for ECMO comes from relatively small randomised controlled trials (RCTs) and observational data. The global ELSO registry of all ECMO cases worldwide [25] is also an important research tool. When reviewing trial data for ECMO, and comparing the practice of different ECMO centres, it is particularly important to consider patient selection, as this has the largest bearing on outcome [1, 26].

Acute respiratory distress syndrome

The most well-established trials of ECMO in the literature are two inconclusive RCTs examining ECMO support in patients with ARDS, first in 2009 and then again in 2018 [6, 12]. Notwithstanding the heterogeneous pathophysiology of ARDS, the CESAR trial, in 2009, randomised 180 patients in the UK with severe but potentially reversible respiratory failure secondary to ARDS to transfer to an ECMO capable specialist severe acute respiratory failure centre, or to remain at their local referring hospital. There were better outcomes including mortality for patients transferred to the specialist centre, but only 76% of those transferred went on to require VV-ECMO, so the trial describes the effectiveness of specialist ECMO capable centre care rather than the effects of ECMO on survival. Of note, the CESAR trial set the standard for inclusion and exclusion criteria adopted by the ELSO guidelines only enrolling patients with severe respiratory failure with a Murray score of $\geqslant$3 or those with uncompensated hypercapnia who were under 65 years of age and had been ventilated for <7 days [6].

The EOLIA trial, in 2018, compared ECMO to volume-controlled ventilation in 249 patients with ARDS across 64 centres, predominantly in France, and found no difference in 60-day mortality. Patients were similar to those in the CESAR trial with a mean age of 52 years. However, the trial was criticised due to 28% crossover between groups in the control arm to ECMO, which would have greatly diluted the ECMO treatment effect. In fact, *post hoc* analysis showed an absolute risks reduction of death from ECMO support in all-comers of between 2% and 20% [12, 27].

There are also a number of large retrospective registry papers showing good outcomes for ECMO in carefully selected patients with ARDS [26].

COVID-19

The management of ARDS came to the forefront of medicine during the global COVID-19 pandemic in early 2020. This was associated with a significant interest in the use of ECMO in COVID-19. After initial observational reports from China showed poor outcomes, concerns were raised about the efficacy of ECMO as a support mechanism in COVID-19 [28]. However, with careful selection of patients, the emergence of effective treatments, including steroids, and an acknowledgment of the requirement for far longer runs than had previously been accepted, ECMO was shown to be as effective for COVID-19 patients as for others with ARDS [29]. Interestingly, as the pandemic continued into the second and third waves patients who had progressed to ARDS despite vaccination or disease modifying treatment fared less well when they deteriorated to need ECMO [30]. One possible explanation for the increased mortality is that these patients were more likely to have treatment-refractory disease, again highlighting the importance of reversibility of the underlying condition as a predictor of ECMO outcomes.

Finally, the results of a retrospective analysis of patients referred to the ECMO service in the UK shed further light on the real-world effectiveness of ECMO in a carefully selected population. This retrospective study showed that patients who were supported on ECMO for COVID-19 had better outcomes than closely matched controls managed with conventional treatments who were referred to the ECMO service but felt to be too well for ECMO [31].

Asthma

Despite being by definition a reversible condition, the death rate for asthma remains high with a yearly mortality of 0.98 per 100 000 people in the USA. Patients with asthma can die from hypoxia or cardiovascular collapse due to acidaemia, tension pneumothorax or right heart failure due to mechanical ventilation [32]. This makes ECMO a potentially attractive support mechanism for these patients, allowing time for resolution of bronchospasm, which normally only takes days rather than weeks.

The main data for asthma in ECMO come from retrospective studies. The most recent data from ELSO in 272 patients with asthma shows that up to 85% of patients survive to decannulation, with an average ECMO run of 7 days and that age, bleeding, higher PEEP and higher post-ECMO driving pressure were all associated with increased mortality [33]. Warren *et al.* [34] demonstrated a survival rate of 95% in patients supported on ECMO for asthma in the UK, highlighting the use of this technology in a small subset of patients with this condition.

Pulmonary embolism

Massive pulmonary embolism causes right heart failure and carries a high mortality. The mainstay of treatment is systemic thrombolysis but a number of guidelines now mention that ECMO could be considered in those cases where standard measures fail [35].

Unlike most other patients presenting with hypoxia patients with pulmonary embolism will be more likely to require both respiratory and cardiac support. This means VA-ECMO is much more widely used in this cohort of patients that with other indications for ECMO, some of whom will require ECPR [36, 37].

V-PA ECMO provides an elegant solution to the problems of isolated right ventricular failure experienced by patients with massive pulmonary embolism. The evidence for the use of this type of ECMO is scant and limited to case reports and series from highly specialised institutions [38]. VV-ECMO has been used extensively in patients with pulmonary embolism. In a retrospective analysis of German patients with pulmonary embolism nearly half of the 2197 supported with ECMO had VV- and not VA-ECMO. VV-ECMO can help patients with pulmonary embolism by reducing pulmonary vascular resistance through the correction of hypoxia and pH leading to improved right ventricular function [36].

ECMO support can stabilise the patient in the hyper-acute phase of pulmonary embolism, but other interventions are often required to reduce the clot burden. These may include anticoagulation, embolectomy and catheter-directed or systemic thrombolysis. Patients supported with ECMO for massive pulmonary embolism seem to have slightly better survival than the general VA-ECMO cohorts with those centres performing surgical embolectomy reporting the best outcomes and those patients requiring ECPR having the worst [37].

Bridge to transplant

ECMO has been used as a bridge to transplant for many years. Those patients already on the transplant list can be successfully supported with ECMO, whilst waiting for suitable donor lungs to become available, with similar outcomes to other populations [39].

The use of ECMO in patients on the transplant list, with rapidly progressive underlying lung conditions, avoids the need for ventilation and sedation. This allows patients to continue to exercise and engage with physiotherapy whilst awaiting their transplant, which seems to be a key feature influencing their post-transplant outcomes [40].

ECMO is also used increasingly as a bridge to decision in patients with chronic respiratory disease (as outlined later in this review), with outcomes similar to those patients who were supported on ECMO who were already on the transplant list at the time of cannulation [41]. Further research is needed in this area to try and define the patients most likely to be accepted for transplant by various international, national and local criteria.

Complications and risks of ECMO

ECMO related complications are common and have limited the application of this treatment in the past (figure 1). With advances in technology, patient selection and emergence of structured multidisciplinary management strategies ECMO complications have reduced significantly over the past 20 years. Despite this ECMO remains a high-risk intervention with several specific and nonspecific complications contributing to a high burden of morbidity and mortality in these patients.

In a systematic review of 23 studies and 12 860 patients the most commonly occurring complications of VV-ECMO were sepsis, multi-organ failure and acute renal failure, each present in ~25% of cases. Cannulation complications were seen in 7% and neurological complications, including stroke and intracranial bleeding, occurred in another 7% [42].

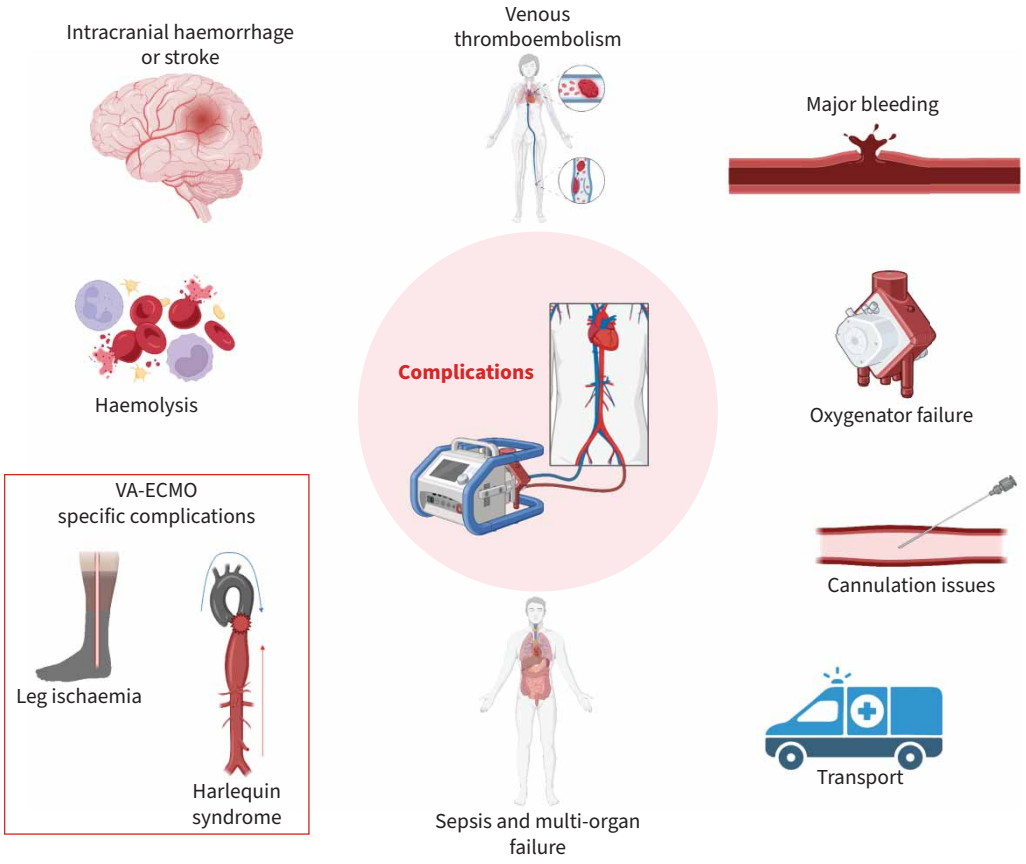


FIGURE 1 Complications of extracorporeal membrane oxygenation (ECMO), including some veno-arterial (VA)-specific complications.

Bleeding is one of the main complications of ECMO. This is generally due to the need for systemic heparinisation and consumption of coagulation factors in the circuit. The risk of bleeding in patients on ECMO is as high as 30%, with a 10% risk of major bleeding needing intervention and a 4–10% risk of intracranial haemorrhage, which in many cases can be devastating [43, 44].

Equally challenging is the increased risk of thrombosis, with venous and arterial embolic phenomenon, including stroke, occurring in nearly a quarter of patients. Circuit failure is a further risk of ECMO support. The oxygenator may clot and need replacing. This is usually undertaken in a controlled way, but occasionally as an emergency, with likely patient deterioration [45].

Other risks include that of haemolysis, cannulation, transport, and the non-resolution of the underlying condition, which all add to the morbidity and mortality that patients on ECMO suffer [46, 47].

While broadly similar, VA-ECMO has a few specific complications that mainly relate to cannulation of the arterial tree and the retrograde flow of blood in the aorta. This includes leg ischaemia due to cannula and artery size mismatch and the issue of differential hypoxia. The latter is known as "Harlequin syndrome", which can only occur in patients supported on VA-ECMO with severe lung disease and some native cardiac output. This combination can result in the lower half of the body being well oxygenated *via* the ECMO circuit, while the upper part of the body including the heart, brain and upper limbs may be rendered hypoxic as blood being ejected by the heart into the upper aorta has not been oxygenated effectively due to the lung disease [46]. Harlequin syndrome may be an indication for hybrid venous-arterial-venous (VAV)-ECMO, which will be discussed later in this review [48].

Many patients supported with ECMO suffer from long-term morbidity even after surviving to hospital discharge. This morbidity relates to the patient's recovery after their critical care stay, their ECMO run and their underlying illness. The sequelae of critical care are now well-established with physical and psychology issues making up the post-intensive care syndrome described by Herridge and Azoulay [49]. ECMO patients with cardiorespiratory disease are likely to suffer some specific complications including scars and neuropraxia from femoral cannulation and persistent changes in pulmonary function and subsequent reduction in exercise tolerance and quality of life [50].

The success of ECMO is in part related to avoidance of the complications detailed above. This requires a large multidisciplinary team of highly skilled nurses, doctors, perfusionists, therapists, physiologists and psychologists with appropriate training, equipment, guidelines and governance to care for all aspects of the ECMO patient and their family [51]. Evidence suggests better outcomes for patients in high-volume ECMO centres with highly skilled multidisciplinary teams managing complex patients as part of an ECMO service [26].

Expanding technology and indications for ECMO in cardiorespiratory disease

Although ECMO is not a panacea for severe cardiorespiratory disease, as ECMO circuits become safer and more widely available new configurations and indications for ECMO have emerged, enabling more patients to benefit from this support mechanism.

Hybrid circuits

The typical VA- and VV-ECMO circuits described so far are adequate support for most patients; however, some patients benefit from a modification to the traditional circuit [8, 48].

In some rare cases of respiratory failure there will be complete cardiovascular collapse due to cardiogenic shock. Examples of this include influenza which can result in both ARDS and myocarditis. Another issue may be that of Harlequin syndrome, as mentioned earlier, when weaning from VA-ECMO. This occurs when resolution of the lung component of the patient's disease lags behind the cardiac component. Under these circumstances the patient may need to be supported with VAV-ECMO where blood is drawn from the venous system and returned to both the arterial and venous trees [47].

Another attractive option is low-flow extracorporeal carbon dioxide removal (ECCO2R), which is essentially ECMO using smaller cannulae with enough flow to remove carbon dioxide but generally adding little in terms of oxygenation. While this technology proved not to be useful in an unselected group of patients with respiratory failure [52], there is emerging evidence for its use in patients with hypercapnic respiratory failure requiring noninvasive ventilation (NIV) [53].

There are many other hybrid circuits which are beyond the scope of this review and pertain to the management of cardiogenic shock from primary cardiac disease [23].

Anticoagulation-free ECMO

Bleeding and clotting have already been described as major complications of ECMO. With advancements in membrane technology, it is now possible to run ECMO circuits without systemic anticoagulation. In one meta-analysis it was demonstrated that spending more than 24 h off anticoagulation (median 4.5 days) whilst supported on ECMO resulted in no significant increase in thrombotic events above baseline. Interestingly, all significant thrombotic events in this cohort occurred in patients supported on VA-ECMO, suggesting that the need for anticoagulation may be dependent on the mode of ECMO support [45]. However, another study showed that anticoagulation can be safely withheld from a population of patients supported on VA-ECMO without another indication for systemic anticoagulation with a reduction in complication rates. This was particularly important for the risk of developing clinically significant bleeding and heparin-induced thrombotic thrombocytopenia [54]. Further studies are required to delineate the optimal anticoagulation strategy for patients on ECMO, but emerging evidence suggests that systemic anticoagulation may become less vital as technology evolves, opening the use of mechanical support to those at higher risk of bleeding.

Emerging indications

The benefits of ECMO in several different cardiorespiratory diseases are expanding and are shown in figure 2.

Chronic lung disease

As mentioned earlier, ECMO in patients with chronic lung disease has generally been reserved for those on the transplant list [41].

In cystic fibrosis, studies have shown that ECMO is a useful support mechanism in patients as both a bridge to transplant and a bridge to decision [55]. With the advent of cystic fibrosis transmembrane conductance regulator (CFTR) treatments [56] there may even be an argument that some patients who are CFTR-naïve or those who have stopped this treatment could be treated with ECMO to enable them to recover from exacerbations that would have previously consigned them to lung transplant or death.

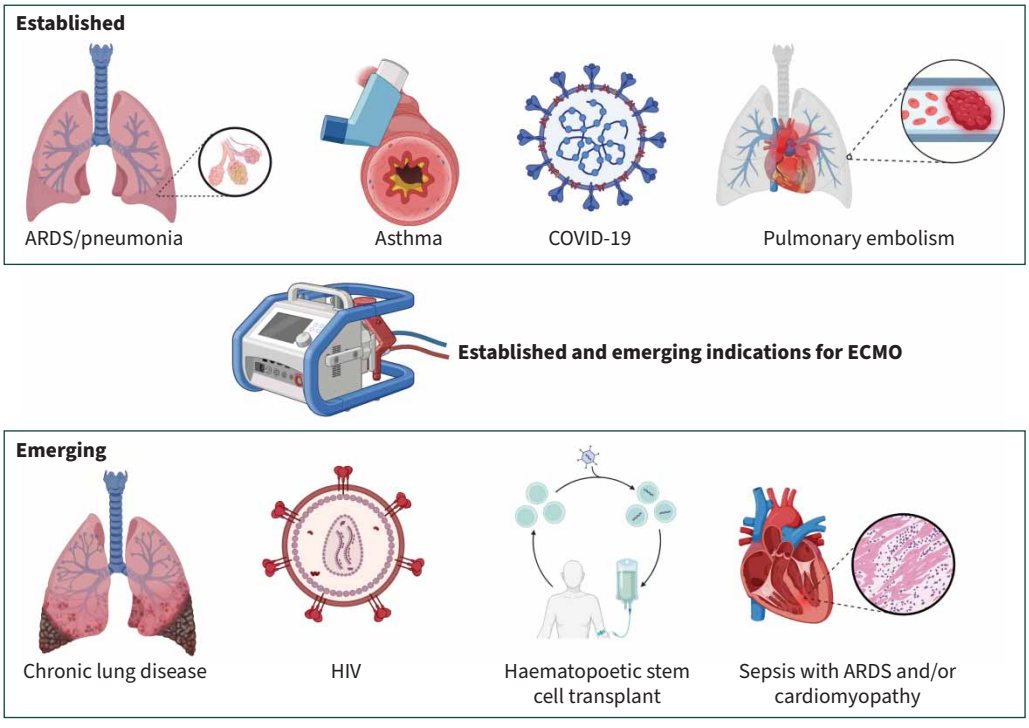


FIGURE 2 Established and emerging indications for extracorporeal membrane oxygenation (ECMO) in patients presenting with hypoxia due cardiorespiratory disease. ARDS: acute respiratory distress syndrome.

Much like in cystic fibrosis, patients with interstitial lung disease (ILD) were traditionally only seen to benefit from ECMO if they were on the lung transplant waiting list [57]. Novel evidence suggests that if patients with ILD can be well supported on ECMO and are suitable for lung transplant, the outcomes for them are as good as those already listed prior to ECMO initiation. Unfortunately, outcomes remain universally poor when transplant is not an option [58].

In COPD, as with other chronic lung diseases, ECMO is an attractive option for bridge to transplant [40]. ECCO2R, described earlier, may also have a role in patients with acute exacerbations of COPD requiring NIV, with a recent pilot trial showing a faster resolution of symptoms and improvement in gas exchange in those on extracorporeal support compared to those supported with NIV, with no mortality or complication difference [53]. Furthermore, a recent study enrolled patients with COPD exacerbations to ECMO or standard care. The ECMO group had quicker resolution of gas exchange abnormalities and lung function compared with controls. The ECMO group did however suffer more complications, prompting the study authors to acknowledge the need for further investigation in this area [59].

Immunosuppression

In the past, immunosuppression has generally been considered a relative contraindication to ECMO. As treatments for patients who are immunosuppressed change so does the potential for the application of ECMO in this cohort. In one large retrospective study of patients who were chronically or acutely immunosuppressed the authors found no difference in ECMO outcomes when compared with immunocompetent controls. In this study immunosuppressed patients were considered as those on immunosuppressant drugs or >20 mg of steroids per day [60].

According to the ELSO registry, patients with HIV supported with ECMO had a worse prognosis that the general population of ECMO patients, with a survival rate of ∼40%. This study did not report data on viral load, CD4 count or prior treatments, making conclusions on which patients, if any, in this cohort may benefit from extracorporeal support challenging [61]. More recent evidence shows that patients newly diagnosed with HIV, who were antiretroviral therapy naïve, had a survival to hospital discharge of ∼90% when supported with ECMO. Although small numbers, most of these patients presented with *Pneumocystis jirovecii* pneumonia, another previously identified poor prognostic marker. This latter study demonstrates that patients with HIV can be well supported on ECMO if there is an intervention, like antiretroviral therapy, that could change the outcome of their underlying disease process [62].

There has also been a step change in the application of ECMO in haematopoietic cell transplantation. A recent consensus statement, published in the *Lancet Respiratory Medicine* [63], suggests that haematopoietic cell transplantation should no longer be an absolute contraindication to ECMO particularly in the late stages and where there is clearly reversible pathology under assessment by a multidisciplinary team. Further work will be needed to determine the effectiveness of ECMO in this population who have previously been shown to have very poor outcomes [63].

Sepsis

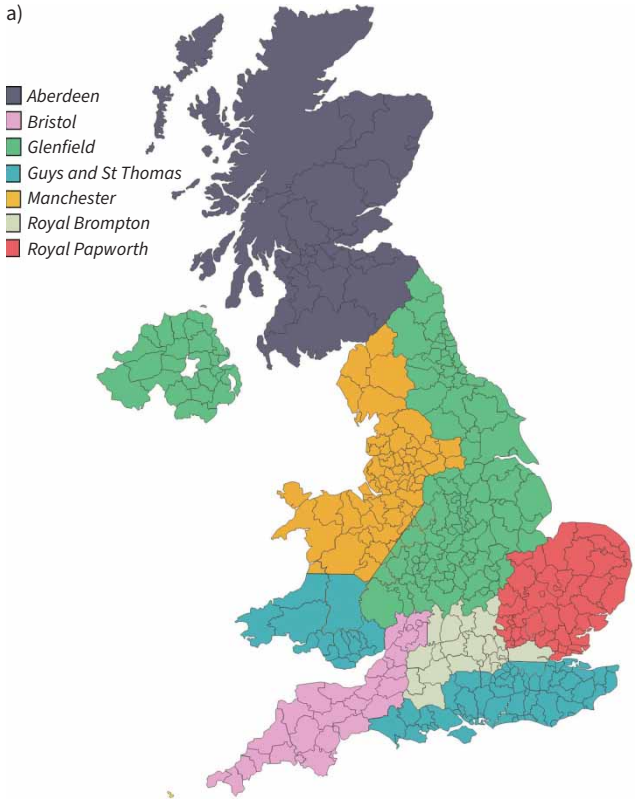
There is an emerging interest in the use of ECMO in patients with sepsis. All modes of support, including VV-, VA- and hybrid VAV-ECMO, have been attempted in this group. In those with hypoxia or hypercapnia driven vasoplegia and right ventricular dysfunction VV-ECMO may significantly stabilise the patient's haemodynamics leading to better outcomes. Most studies in patients with preserved ventricular function and distributive shock demonstrate that VA-ECMO confers no survival benefit. This contrasts with those patients who have a septic cardiomyopathy with reduced ejection fraction, where VA-ECMO or VAV-ECMO may confer a survival benefit [64, 65]. In one small study, patients with septic cardiomyopathy and ARDS supported on VAV-ECMO had a 75% survival rate, in part due to the rapid resolution of the underlying condition with appropriate antibiotic treatment [66].

ECMO delivery: an example of a national ECMO network from the UK

As mentioned previously, a strong multidisciplinary team approach, with strict governance practice and high volumes of patients improves ECMO outcomes. In the UK there is a nationally commissioned ECMO service consisting of seven ECMO centres and three surge centres for patients with respiratory failure secondary to cardiorespiratory disease (figure 3a). There are established criteria for eligibility for VV-ECMO that have been adopted by this network [67]. These are detailed in figure 3b.

With these guidelines, historically, as a network the UK was able to achieve survival rates of 75% to intensive care unit discharge. It was also able to able to maintain these outcomes with similar survival rates during the COVID-19 pandemic, despite a requirement for an increase in ECMO capacity of nearly 600% [34, 68].

a)



b)

Eligibility criteria:
ECMO is a bridge to recovery and reversibility of the presenting condition is a key criterion for inclusion in the service. Reversibility will be based on expert clinical opinion.

Bridging to transplant is not part of this service specification.

Inclusion criteria:
- Patients with demonstratable severe respiratory failure from non-cardiac cause (*i.e.* Murray Lung Injury score 3.0 or uncompensated hypercapnia with a pH <7.2 despite optimal conventional management)
- Patients for whom ongoing positive pressure ventilation is not appropriate (*e.g.* significant tracheal injury)

Exclusion criteria:
- Patients with contraindications to continuation of active treatment
- Patients with significant comorbidity likely to lead to dependency to ECMO support (profound muscle weakness, significant irreversible pulmonary fibrosis due to underlying condition or duration of mechanical ventilation)
- Patients with significant life-limiting comorbidity (*e.g.* severely immunocompromised patient, advanced malignancy)

FIGURE 3 a) Geographic distribution of the UK National Health Service extracorporeal membrane oxygenation (ECMO) network across England and Scotland. b) UK commissioning criteria for ECMO 2019 [67]. a) Map courtesy of © Copyright Bruce Jones Design 2024.

As well as improving equity of access to ECMO support and delivering excellent outcomes, the ECMO network in the UK has been instrumental in standardising care according to best practice and being at the cutting edge of ECMO research. Examples of this include the production and publication of guidelines for allied healthcare professionals, bench-marking against standards published in a national intensive care database and the securing of cross-network funding to determine the optimal ventilatory settings during a VV-ECMO run [69, 70].

Future ECMO research

There are 120 adult ECMO studies currently registered on clinicaltrials.gov. The focus of these studies vary from predictors of mortality to biological effects of membrane oxygenators on the microbiome. Areas for future research in adult ECMO for cardiorespiratory disease will include the following topics.

- Improvements in membrane technology to reduce complications.
- Reducing the need for anticoagulation to decrease the risk of bleeding.
- The use of ECMO in new configurations and in new conditions or indications.
- The influence of ECMO on inflammation in the lungs.
- Pulsatile ECMO to improve microcirculatory perfusion.
- The optimum ventilator strategy on VV-ECMO.
- Patient selection for VA-ECMO and hybrid ECMO.
- Long-term outcomes in ECMO survivorship beyond survival.

We hope these areas of research will inform better application of this technology to enable clinicians to effectively treat more patients and achieve better outcomes [71].

Conclusions

ECMO for respiratory failure caused by cardiorespiratory disease has advanced massively over the past 35 years. While evidence from RCTs is lacking, in the right circumstances ECMO can be a life-saving intervention. Patient selection and avoidance of complications by multidisciplinary working and research will help to define and refine the use of ECMO in at-risk populations in the future.

Key points

- ECMO can provide support for carefully selected patients with reversible cardiorespiratory disease or can be used as a bridge to transplant.
- The evidence for ECMO in cardiorespiratory disease is limited to a small number of RCTs and registry data.
- Despite this, with careful multidisciplinary management, the use of ECMO is expanding with better outcomes and novel approaches for patients with cardiorespiratory disease.

Self-evaluation questions

1. ECMO should be considered when the perceived mortality from a condition reaches:
    a) 20%
    b) 25%
    c) 50%
    d) 60%
    e) 75%
2. All the following are relative or absolute contraindications to ECMO except:
    a) Platelet count <20×10^9 per L
    b) Age >60 years
    c) Acute haemorrhagic stroke
    d) Exacerbation of interstitial lung disease not suitable for transplant
    e) Inability to cannulate
3. Which one of the following statements about ECMO in COVID-19 is true?
    a) COVID-19 outcomes on ECMO were significantly worse than those pre-COVID
    b) Mortality from COVID-19 in patients supported on ECMO decreased over time
    c) COVID-19 patients needed longer ECMO runs than patients presenting previously with viral pneumonia
    d) COVID-19 is a contraindication to ECMO
    e) All patients with COVID-19 need V-PA ECMO due the right ventricular dysfunction associated with the condition
4. All the following statements about Harlequin syndrome are true except:
    a) It is the reason that all patients on VA-ECMO should have a right radial arterial line
    b) It can result in cardiac ischaemia
    c) It can only occur when there is lung disease
    d) It can herald myocardial recovery in patients with cardiogenic shock
    e) It can be treated by decreasing ECMO flows

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Suggested answers

1. c.
2. b.
3. c.
4. e.