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REVIEW

Venovenous extracorporeal membrane oxygenation for acute respiratory failure

A clinical review from an international group of experts

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Abstract

Despite expensive life-sustaining interventions delivered in the ICU, mortality and morbidity in patients with acute respiratory failure (ARF) remain unacceptably high. Extracorporeal membrane oxygenation (ECMO) has emerged as a promising intervention that may provide more efficacious supportive care to these patients. Improvements in technology have made ECMO safer and easier to use, allowing for the potential of more widespread application in patients with ARF. A greater appreciation of the complications associated with the placement of an artificial airway and mechanical ventilation has led clinicians and researchers to seek viable alternatives to providing supportive care in these patients. Thus, this review will summarize the current knowledge regarding the use of venovenous (VV)-ECMO for ARF and describe some of the recent controversies in the field, such as mechanical ventilation, anticoagulation and transfusion therapy, and ethical concerns in patients supported with VV-ECMO.

Keywords: Critical care, Extracorporeal membrane oxygenation, Intensive care units, Respiratory distress syndrome, adult, Respiratory failure, Review, Ventilation, artificial

Introduction

Despite expensive life-sustaining interventions delivered in the ICU, such as mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO), mortality in patients with acute respiratory failure (ARF) remains unacceptably high. ECMO has emerged as a promising intervention that may provide more efficacious supportive care to these patients. Improvements in technology have made ECMO safer and easier to use, allowing for the potential of more widespread application in patients with ARF. A greater appreciation of the complications associated with the placement of an artificial airway and MV has led clinicians and researchers to seek viable alternatives to providing supportive care in these patients.

Overview

ECMO for ARF was first applied in 1966 and reported by Hill et al. [1]. The ECMO in this first experience was venoarterial (VA) bypass. This form of respiratory assistance was applied in the majority of the 266 cases reported in a systematic review (1966–1975) of ECMO support [2]. Only 11 % of the cases were supported in venovenous (VV) mode. In addition, the first randomized trial on ECMO in adults with severe ARF involving nine centers in the USA [3] also used VA-ECMO in the treated patients. The high mortality rate observed in both groups led most centers to abandon this technique and enthusiasm for ECMO in adults was subdued for many years.

As the majority of ARF patients require pulmonary support only, VV-ECMO is the preferred configuration,

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allowing preserved lung perfusion and more homogeneous systemic oxygenation, without the added risks of arterial access, increased cardiac afterload, and decreased cerebral blood flow that may occur with VA-ECMO, which also provides cardiac support. Thus, this review will summarize the current knowledge regarding the use of VV-ECMO for ARF and describe some of the recent controversies in the field, such as MV, anticoagulation and transfusion therapy, and ethical concerns in patients supported with VV-ECMO.

Physiological basis of VV-ECMO

Most of the metabolically produced CO_2 may be eliminated using just 1–1.5 L of blood flow in an extracorporeal circuit. In fact, given the high CO_2 content in the blood (assuming a normal pH and PCO_2, CO_2 content is about 45–50 mL/100 mL blood), theoretically clearing 100 % of VCO_2 from approximately 500 mL/min of blood would match the metabolic CO_2 production per minute. Removing 100 % of the CO_2 produced may lead to complete apnea in the spontaneously breathing patient. Oxygenation, in this extreme form of ventilatory support, may be provided by continuous 100 % oxygen flow into the native lung [4]. However, when ventilation is sharply decreased the mean airway pressure also decreases and positive end-expiratory pressure (PEEP) must be applied to maintain lung volume. In normal lambs [5] the pressure necessary to avoid partial collapse is approximately 20 cmH_2O. In addition, if the artificial lung is being ventilated with 100 % oxygen and the native lung is being ventilated with a fraction of inspired oxygen (FiO_2) lower than 100 %, nitrogen will transfer from the alveoli to the blood increasing the likelihood of reabsorption atelectasis in the absence of a sufficient PEEP level [4]. If the same FiO_2 is used in both the native and artificial lungs, this problem can be minimized. In addition, if the same $PaCO_2$ has to be maintained during extracorporeal support, the alveolar ventilation must be decreased proportionally to the CO_2 being removed by ECMO [6].

While CO_2 removal can be completely performed by the artificial lung, oxygenation depends on the relative contribution of the residual gas exchanging part of the native (baby) lung and of the artificial lung (Fig. 1). In VV-ECMO, the two systems are placed in series and the performance of the artificial lung affects the native lung. Two important points have to be remembered. First, the greater the contribution of oxygen by the artificial lung resulting in higher mixed venous oxygen saturation (SvO_2), the lower is the transfer of oxygen from the native lung. Thus, if SvO_2 reached 100 %, the transfer of oxygen from the native lung would be zero. Therefore, the improvement of arterial oxygenation during VV bypass is due to increased oxygen content in the blood flowing through shunted areas. Second, the shunt fraction may increase at the beginning of VV bypass. As SvO_2 increases, any residual hypoxic vasoconstriction may be lost [7], with more blood perfusing the shunted areas and less blood perfusing the residual healthy native lung [8]. The final result is an improvement in oxygenation which could be limited to few points of arterial oxygen saturation when the bypass begins (Fig. 2) [9].

Indications for VV-ECMO

VV-ECMO can be used as a life-saving rescue therapy in patients with ARF when MV cannot maintain adequate oxygenation or CO_2 elimination (Fig. 3) [10–12]. Such situations might be encountered in the most severe forms of the acute respiratory distress syndrome (ARDS) [13–15], or in severe asthma [16]. Alternatively, VV-ECMO may be used in patients in whom the cost of maintaining adequate oxygenation is too high, resulting in an unacceptably high risk of ventilator-induced lung injury (VILI). In this case the goal of ECMO is to allow "lung rest" by lowering airway pressures and tidal volume rather than improving oxygenation per se [11, 17]. Other indications include patients undergoing lung transplantation [18] (as a bridge to surgery or after complicated operation), or those with severe air leak syndromes. In circumstances where there is concomitant cardiac failure, such as in severe viral infections with pneumonia and myocarditis, there may be a need to consider VA-ECMO, alone or in combination with VV-ECMO.

Contraindications for VV-ECMO

Absolute contraindications

Absolute contraindications to ECMO are moribund patients with established multiple organ failure, those with poor short-term prognosis (e.g., metastatic malignancy) or other advanced comorbidities such as chronic respiratory insufficiency with no indication for transplantation or irreversible, devastating neurological pathology (e.g., massive intracranial hemorrhage).

Relative contraindications

Traditionally, relative contraindications are high pressure MV for more than 7 days, advanced age, limited vascular access, bleeding, and contraindications to limited (i.e., subtherapeutic) anticoagulation. Under certain circumstances, VV-ECMO can be run without anticoagulation. Since ARDS patients treated in low case volume ECMO centers were reported to have poorer outcomes [19], the annual volume for the entire center should, with limited exceptions, be at least 20 cases per year, with a minimum of 12 ECMO cases for adult ARF per year [10]. Thus, patients should be referred to high case volume ECMO centers where possible. For additional information on the

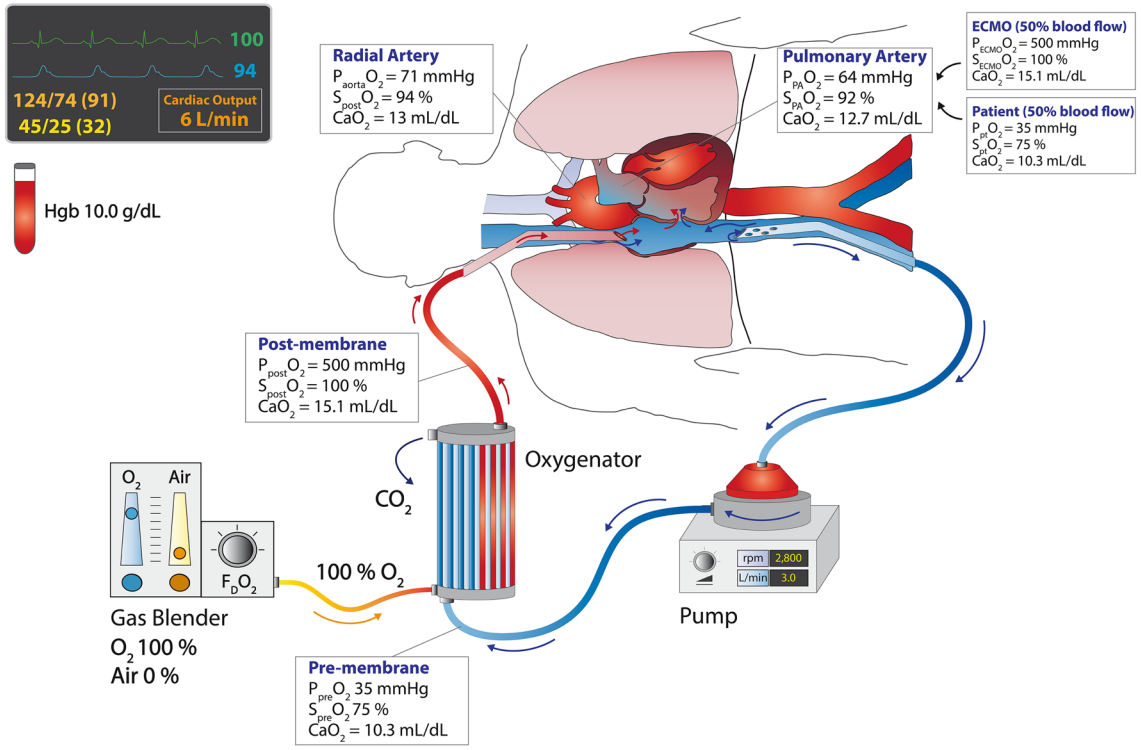

Fig. 1 Venovenous extracorporeal membrane oxygenation circuit

organization of ECMO centers, including nurse staffing and mobile ECMO units, please see the Electronic Supplementary Material.

Cannulation for VV-ECMO

Single lumen cannulae

Single lumen cannulae, with one for drainage and one for reinfusion, are a common way of providing VV-ECMO support in adults. The larger the venous drainage cannula the higher the flow that is possible, which may be needed (i.e., 29–31 Fr for >6 L/min blood flow) in cases of profound hypoxemia in severe ARDS. It is possible to drain from either jugular vein and either femoral vein, the site of the reinfusion cannula will determine the amount of recirculation, and total oxygen delivery will depend on the balance between venous oxygen saturation, recirculation, and total possible extracorporeal flow. The best configuration is femoral drainage (with the tip positioned in the right atrium for maximal drainage) and jugular reinfusion (with a short cannula) [20]. If using a bigger venous drainage cannula, greater oxygen delivery (in the presence of greater recirculation) is possible with right jugular drainage and femoral reinfusion [21]. The least effective setup is femoral–femoral, in which there are two possible configurations: either draining from the right atrium and reinfusing into the iliac (long drainage, short reinfusion) which can result in up to 60 % recirculation; or the converse which has almost zero recirculation but limited venous drainage. Despite these theoretical limitations, it is possible to support patients effectively using the femoral–femoral approach. In some instances, drainage with a single cannula may be insufficient to generate adequate blood flow; in this case, a second, additional drainage cannula may be required [13]. The best

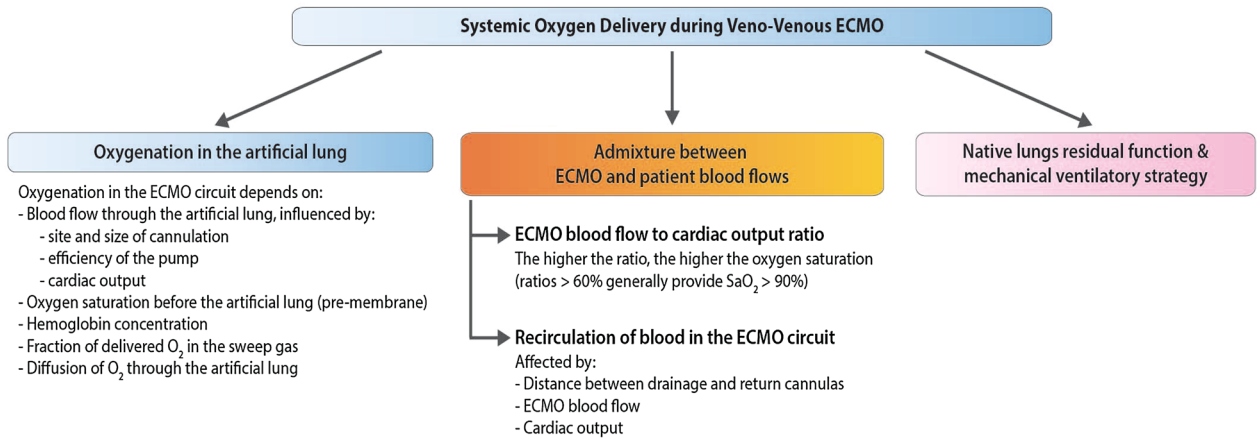

Fig. 2 Factors contributing to systemic oxygen delivery during venovenous ECMO

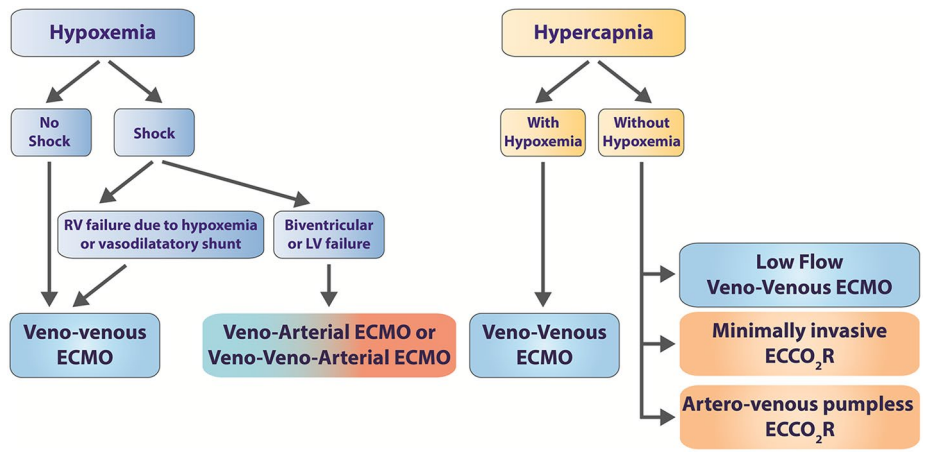

Fig. 3 A potential approach to the use of extracorporeal support modalities in the management of acute respiratory failure. *ECMO* extracorporeal membrane oxygenation, *ECCO2R* extracorporeal CO2 removal, *LV* left ventricle, *RV* right ventricle

configuration for this is drainage from the superior vena cava (SVC)/right atrial junction via the right internal jugular vein and from the left common iliac vein via the left femoral with reinfusion into the inferior vena cava (IVC) with a cannula inserted 40 cm via the right femoral vein. Other three-cannula configurations will also work.

Double lumen cannula

There are two types of double lumen cannula which are suitable for adult ECMO, the bicaval Avalon Elite (Maquet Holding B.V. and Co. KG; Rastatt, Germany) cannula and the right atrial OriGen (OriGen Biomedical GmbH; Burladingen, Germany) cannula. Both are designed to be inserted percutaneously via the right internal jugular vein; however, other sites may be considered (e.g., subclavian vein). The Avalon cannula requires imaging (fluoroscopy or echocardiography) to achieve the correct bicaval placement with one drainage lumen in the IVC and the reinfusion port in the right atrium. The advantage of fluoroscopy is the ability to see the whole wire in one image, which reduces the chances of a loop forming across the tricuspid valve. The bicaval design promotes very low recirculation and the neck position allows easier mobilization of the patient. The OriGen

cannula is a right atrial design and is therefore much easier to insert. The right atrial design means that there will be more recirculation and the flow must be adjusted accordingly.

Who should cannulate?

An operator with appropriate skills should cannulate; these skills include a thorough knowledge of ECMO, the ability to perform procedures aseptically, expertise in percutaneous access, and the ability to interpret the imaging modality to be used. Clearly it is possible for intensivists, interventional radiologists, cardiologists, anesthesiologists, and surgeons to cannulate successfully. Sometimes it is not possible to have all of these skills in one person and a team approach must be used. In addition, if the operator is not a cardiothoracic surgeon there must be a proactively arranged procedure for dealing with complications when they arise, although it is realistic to recognize that the chances of saving a patient from a major cannulation disaster are remote. The cannulation team should be limited to a manageable number in order to maintain individual operator skills and to allow audit and benchmarking against accepted practice standards.

Complications of VV-ECMO

Complications during ECMO are common and potentially life-threatening (Table 1); therefore, it is of cardinal importance to know, recognize, and treat complications of ECMO at the earliest possible moment.

Complications of cannulation

As large cannulae (up to 32 Fr) are used for VV-ECMO and implantation can cause many problems, cannulation should be performed by experienced operators with high-quality equipment. While the incidence of deep venous thrombosis (DVT) complicating ECMO is not precisely known, it is likely underdiagnosed [22, 23]. Serial investigations for DVT after VV-ECMO reveal an incidence of nearly 20 % (T. Muller, unpublished data) [24]. Prevention of DVT is one of the main indications for systemic anticoagulation of ECMO patients. Systematic ultrasound screening should be done after decannulation, and anticoagulation continued if indicated. As DVT is not uncommon, and its sequelae may be life-threatening, further research is urgently needed.

Technical complications

Technical failure of modern ECMO systems is less common in comparison to older ECMO systems. Still, mechanical or electrical failure can occur and can result in a medical emergency with need for rapid exchange of the system. A recent report of 265 adult patients on VV-ECMO found a need for exchange (e.g., pump head/oxygenator thrombosis, worsening gas exchange) in 83 patients; 45 % of these were acute, 55 % elective exchanges [25]. Contamination and colonization of membrane oxygenators in septic patients have been described and can be associated with hyperfibrinolysis and bleeding [26].

Thrombosis and bleeding

Little is known about the occurrence of heparin-induced thrombocytopenia (HIT) in VV-ECMO patients [27]. Many experts agree that HIT can complicate ECMO therapy and carries a high risk of thrombosis both in the patient and in the system. Therefore, change to an

Table 1 Complications and considerations with ECMO in adults with respiratory failure

Complication	Considerations
Cannulation	*ELSO Registry reports 6 % of cases have cannulation-related complications* Should be performed by experience operators, using ultrasound or fluoroscopy for guidance As cannulation-associated injury can rapidly lead to life-threatening complications, adequate blood products (e.g., PRBCs) should be readily available Careful handling of guidewire to minimize risk of cardiac perforation or retroperitoneal injury Vessel injury, serious bleeding, cannulation of improper vessels, venous thrombosis, or advancement of the tip of the cannula into a small side branch of main vessel are other possibilities Care must be taken to fix cannula properly to prevent accidental dislocation Air embolism could be life-threatening and must be avoided Infection of cannula sites can be reduced by sterile percutaneous implantation without skin incision and meticulous nursing care
Technical	*ELSO Registry reports oxygenator failure in 10 % of cases* Polymethylpentene membranes and centrifugaul pumps in modern circuits have practically eliminated plasma leakage, overheating of pump head, and tubing rupture
Thrombosis and bleeding	*ELSO Registry reports 3.8 % incidence of intracerebral bleeding in adults patients on VV-ECMO* Minor hemolysis is commonly observed during VV-ECMO Activation and destruction of platelets by foreign surface of circuit is common and is one risk for increased risk of bleeding on ECMO

ELSO Extracorporeal Life Support Organization, *PRBC* packed red blood cells, *VV-ECMO* venovenous extracorporeal membrane oxygenation

alternative anticoagulation regime (e.g., argatroban) is advisable if HIT is suspected. However, a positive ELISA test for platelet factor 4 antibodies has a high false positive rate, and a platelet aggregation test should be added to confirm the diagnosis.

Minor hemolysis commonly is observed during VV-ECMO. A recent study of 184 adult ECMO patients reported low-level hemolysis (plasma-free hemoglobin 0.1–0.5 g/L) in 99 patients; 24 patients, mainly on VV-ECMO, developed high-level hemolysis (plasma-free hemoglobin >0.5 g/L) [28]. More data are needed to investigate the causes of hemolysis on ECMO and to elucidate its influence on morbidity and mortality. Weingart et al. reported a drop in platelet counts to 60 % of pre-ECMO levels, which was not seen in patients treated with a pumpless arteriovenous (AV) CO_2 removal device [29].

VV-ECMO and outcomes in patients with ARDS

Short-term outcomes

The use of ECMO for severe ARF remains controversial, with conflicting data regarding its impact on survival compared with standard lung-protective MV (Table 2). The CESAR trial evaluated a strategy of transfer to a single center which had ECMO capability, while the patients randomized to the control group were treated conventionally at designated treatment centers [30]. The primary endpoint of 6-month mortality or severe disability was significantly lower for the 90 patients randomized to the ECMO group (37 vs. 53 %, $p = 0.03$). However, 22 patients randomized to the ECMO group did not receive ECMO (e.g., died before or during transport, improved with conventional management at the referral center). Moreover, no standardized protocol for lung-protective MV existed in the control group and the time spent with lung-protective MV was significantly higher in the ECMO group. VV-ECMO was also successfully used for H1N1-associated ARDS. Outcomes from the Australia and New Zealand collaborative group (ANZICS) [13], a UK collaborative cohort series [14], H1N1 patients treated in French ICUs of the REVA Network [15], and the ad hoc Italian ECMO network [31] also reported good outcomes considering disease severity at ECMO initiation.

Non-randomized studies of ECMO, including propensity-matched case–control studies, are prone to important selection biases weakening their interpretation. Coupled with the fact that the CESAR trial had important methodological limitations, more evidence is needed before considering wide adoption of VV-ECMO for severe ARDS patients. The ongoing international multicenter randomized Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial (ClinicalTrials.gov NCT01470703) will test

Table 2 Short-term outcomes in ARDS patients supported with VV-ECMO

Study	Number of patients	Notes
ANZ ECMO Investigators [13]	68	Severe H1N1-associated ARDS (median P/F ratio 56 mmHg, PEEP 18 cmH_2O, LIS 3.8) 25 % ICU mortality
Noah et al. [14]	80	86 % of ECMO-referred patients with H1N1-associated ARDS received ECMO in 4 adult ECMO centers in the UK 24 % hospital mortality (for matched ECMO-referred patients) After matching 75 ECMO-referred vs. non-ECMO-referred patients (GenMatch), mortality was significantly lower in ECMO-referred patients (RR 0.47; 95 % CI 0.31–0.72)
Pappalardo et al. [70]	60	Severe H1N1-associated ARDS (mean age 40 years, PEEP 16 cmH_2O) from Italian ECMOnet 32 % hospital mortality
Peek et al. [30]	180	Lower 6-month mortality or severe disability for patients randomized to ECMO group (37 vs. 53 %, $p = 0.03$) 22 patients randomized to ECMO group did not receive ECMO [e.g., died before or during transport, improved with conventional management at referral center (73 % of these patients)] No standardized protocol for lung-protective MV existed in control group and use of lung-protective MV was significantly greater in the ECMO group
Pham et al. [15]	123	Severe H1N1-associated ARDS (mean P/F ratio 63 mmHg, PEEP 13 cmH_2O, LIS 3.4) from French REVA Network 36 % ICU mortality After propensity score matching of 52 ECMO patients with non-ECMO patients, mortality was not significantly different between groups (OR 1.48; 95 % CI 0.68–3.23) The 51 unmatched patients were younger, had lower P/F ratio, higher Pplat, and lower ICU mortality than matched patients (22 vs 50 %, $p < 0.01$)

CI confidence interval, *CRP* C-reactive protein, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *LIS* Lung Injury Score, *P/F ratio* partial pressure of arterial oxygen to fraction of inspired oxygen ratio, *MV* mechanical ventilation, *OR* odds ratio, *PEEP* positive end-expiratory pressure, *Pplat* plateau pressure, *RR* relative risk

the efficacy of early VV-ECMO in patients with severe ARDS using highly protocolized MV and systematic recourse to prone positioning in the control group [32].

Long-term outcomes

There are few studies of long-term outcome in adult ECMO patients. Frenckner et al. reported long-term outcome in 21 patients for the first time [17]. Most of them had limited fibrosis lesions on CT scan while respiratory function tests were within normal limits. Similarly, patients in the CESAR trial [30] or those with H1N1-associated ARDS supported with ECMO had similar or better quality of life compared with conventionally managed ARDS patients [30, 33]. However it is worth remembering that 1-year quality of life in ECMO patients was poorer than a sex-and age-matched general population [10]. Lastly, significant long-term physical and psychological impairments have been demonstrated in 84 ECMO survivors at 6-month follow-up [34]. The results revealed satisfactory mental health but persistent physical and emotional-related difficulties, such as anxiety (34 %), depression (25 %), or post-traumatic stress disorder (16 %) symptoms. In addition, 36 % of these patients reported exertional dyspnea, with 30 % still receiving pulmonary treatments after a median of 17-month follow-up. There is the need for additional studies to better understand the long-term sequelae of VV-ECMO in patients with ARDS.

Risk factors for death and prognostic scoring systems in VV-ECMO

Hospital mortality for severe ARDS treated with ECMO has ranged between 29 and 43 % in recent cohorts [13, 30, 34, 35]. A high rate of complications and significant long-term physical and neuropsychological impairment [36, 37] have prompted the defining of pre-ECMO risk factors for death in these patients (Table 3). Older age and pre-ECMO comorbidities, such as an immunocompromised status, were consistently associated with increased mortality and should therefore be considered in the decision to initiate ECMO. A duration of MV of at least 7 days prior to ECMO initiation has been associated with a poorer outcome, whereas prone positioning and the use of neuromuscular blocking agents prior to ECMO were both protective in two studies [34, 35]. Although refractory hypoxemia is a frequent indication for ECMO in ARDS, very low pre-ECMO pulmonary compliance (i.e, plateau pressure <30 cmH_2O and inability to increase PEEP above 10 cmH_2O) were both independent risk factors for mortality [3]. Lastly, a greater degree of organ failure was frequently associated with poor outcomes as well [34, 35, 37, 38].

Specific management of the patient supported with VV-ECMO

Mechanical ventilation

MV during VV-ECMO for ARDS has different objectives that depend on the efficacy of the ECMO system, the indication for extracorporeal circulation, and the stage of the disease. The main goals of ECMO are to provide adequate oxygenation and CO_2 elimination, as well as to allow the lung to rest and hopefully to heal [39]. Lung rest means providing less MV, with lower driving pressure and plateau pressure as well as lower respiratory rate and FiO_2.

Three challenges can be observed during MV:

1. If the VV-ECMO blood flow rate is insufficient and the patient is in a hyperdynamic state with a high cardiac output, a substantial portion of the cardiac output may still reach the native lung with a low oxygen saturation, not having gone first through the artificial lung with resulting poor arterial oxygenation. This may be solved by using large venous cannulae allowing for high ECMO flows (>4 L/min), but it may also be the reason clinicians continue using non-protective MV. It may also explain why plateau pressure during VV-ECMO was a strong predictor of outcome [15].
2. The second challenge is to continue delivering some MV as a way to maintain the lung mildly ventilated and open, and avoid complete lung collapse. Complete collapse of the lung during VV-ECMO may be associated with longer recovery times, although there are no rigorous data to support this. Some degree of ventilation while maintaining a sufficient PEEP level (>10 cmH_2O) may be recommended, using plateau pressure $\leq$25 cmH_2O and driving pressures <15 cmH_2O [40]. These MV settings may result in extremely small tidal volumes in many patients that do not result in effective gas exchange. A continuous flow of oxygen to counterbalance the oxygen uptake by the lung and avoid atelectasis may be used [41, 42]. A recent observational study suggested that the use of a higher PEEP during ECMO (at least during the first 3 days) was associated with improved survival [43]. Although we cannot make causal inferences from these observational studies, they tend to support the concept that keeping part of the lung open with reasonable levels of PEEP is important. Some groups have also recommended using low respiratory rates (<10–15 breaths/min), since "ventilation" of the native lung does not generate efficient CO_2 elimination. There is ongoing uncertainty about how best to keep the lung open and the best trade-off between lung protection and lung reopening is there-

Table 3 Prognostic scoring systems in VV-ECMO

Name	Variables	Notes
Italian ECMOnet *N* = 60 [70]	Hospital stay before ECMO Creatinine Bilirubin *Mean arterial pressure*	ROC 0.86 (95 % CI 0.75–0.96) Patients with H1N1 (derivation cohort) and international patients with H1N1 (external validation)
PRESERVE *N* = 140 [34]	Age Immunocompromised Days of MV before ECMO BMI < 30 Pplat > 30 cmH_2O PEEP < 10 cmH_2O SOFA score *Prone positioning*	ROC 0.89 (95 % CI 0.83–0.94) Included quality of life assessment
Marseille score *N* = 85 [38]	Age SOFA score *Influenza pneumonia*	ROC 0.82 (95 % CI 0.71–0.89) Patients mainly from external referrals
Regensburg score *N* = 304 [71]	Age Immunocompromised Minute ventilation *Pre-ECMO hemoglobin* Day 1 FiO_2 Day 1 norepinephrine *Day 1 fibrinogen* Day 1 CRP	ROC 0.79 (95 % CI 0.74–0.85) Regensburg registry (derivation cohort) and comparison with SOFA, ECMOnet, and PRESERVE scores
RESP score *N* = 2355 [35]	Age Immunocompromised Days of MV before ECMO Diagnosis group Acute associated infection PIP Neurological dysfunction Bicarbonate infusion $PaCO_2$ Nitric oxide Cardiac arrest *Neuromuscular blockade*	ROC 0.73 (95 % CI 0.71–0.75) ELSO Registry (derivation cohort) and PRESERVE cohort (external validation)

Adapted from ref. [67]. Variables in italics are associated with a better prognosis

CI confidence interval, *CRP* C-reactive protein, *ECMO* extracorporeal membrane oxygenation, *ELSO* Extracorporeal Life Support Organization, *FiO_2* fraction of inspired oxygen, *MV* mechanical ventilation, *$PaCO_2$* partial pressure of arterial carbon dioxide, *PEEP* positive end-expiratory pressure, *PIP* peak inspiratory pressure, *ROC* receiver operating characteristic curve, *SOFA* Sequential Organ Failure Assessment

fore difficult to define. It is important to remember that plateau and/or driving pressures remain important determinants of outcome during ECMO if substantial MV is delivered [44].

3. When the patient is stabilized, some spontaneous breathing activity may be desirable as a way to exert respiratory muscles. This may be difficult because the drive of the patient may be high, including stimulation from the lungs (e.g., pulmonary "irritant" receptors) for a substantial part. However control of CO_2 elimination with the extracorporeal circuit and the sweep gas flow usually allows control of this respiratory drive [45]. The other reason why this may be challenging is the poor respiratory mechanics of the lungs, making the use of modes like pressure support ventilation very difficult to use. In this situation, interesting results have been reported with the use of neurally adjusted ventilatory assist (NAVA) [46, 47]. NAVA could achieve two important goals: minimizing asynchronies (especially double triggering) in these patients with severe restrictive lung disease and short respiratory system time constants, and allowing the patient to take control of the breathing pattern. Manipulating CO_2 elimination will then act as an external modulator of this drive to breath. No recommendations can be made, however, from these small studies.

In clinical practice, clinicians use a lung-protective MV approach much more often than a recruitment approach and later decide to prioritize weaning VV-ECMO over MV [48, 49]. The optimal approach to MV during VV-ECMO remains unclear and is based on important but anecdotal clinical observations, but will be the focus of ongoing and planned clinical studies in the near future.

Anticoagulation

Anticoagulation during ECMO has been shifting over time with incremental changes in technology and clinical practice, particularly with the use of coated circuits, which decrease—and, at times, perhaps eliminate—the need for anticoagulation to maintain circuit patency. Taking into account the overall decrease in hemolysis and disseminated intravascular coagulation (DIC) seen with modern circuits [50], the concomitant decrease in the need for anticoagulation results in decreased bleeding and therefore decreased transfusion needs. However, how much anticoagulation is needed to maintain circuit patency and avoid DVT in the cannulated veins will vary according to an individual patient's coagulation status. These risks must be weighed against the risk of bleeding with too much anticoagulation. As a result, practices vary widely [51, 52].

A comprehensive guideline for the use and monitoring of anticoagulation during VV-ECMO may be found on the ELSO website (http://www.elsonet.org). This guideline stops short of any one mandate, given the lack of evidence in favor of most of the practices reviewed. With all the uncertainty surrounding the use of anticoagulation during VV-ECMO, what seems clear is that modern circuits permit lowering the effective dose of anticoagulation, with recent reports including the avoidance of anticoagulation for as long as 20 consecutive days [53] in the setting of severe bleeding. However, successful use of anticoagulation in patients with severe bleeding who are receiving VV-ECMO may also be possible [54, 55]. Rigorous evaluations of anticoagulation use in VV-ECMO are needed. In the meantime, centers should follow internal protocols for the use and monitoring of anticoagulation in this setting.

Transfusions

The threshold for transfusing packed red blood cells (PRBCs) in patients receiving ECMO, particularly in the setting of hypoxemic respiratory failure, has traditionally been set in order to maintain hemoglobin in the normal range (120–140 g/L) [56]. However, more recently, this notion has been challenged [11, 57]. Several case series have offered data suggesting that lower transfusion thresholds or administration of fewer units of PRBCs overall may be acceptable as these practices may be associated with good outcomes [13, 29, 58, 59].

In a report of 38 patients with severe ARDS receiving ECMO, a blood conservation protocol consisting of a hemoglobin transfusion threshold of 70 g/L, anticoagulation with a target activated partial thromboplastin time (aPTT) 40–60 s, and autotransfusion of the circuit blood during decannulation resulted in fewer than two-thirds of patients requiring transfusion of PRBCs at any time during their ECMO run and a median of 0.11 units of PRBCs transfused per day while receiving ECMO. Survival to hospital discharge in this series was 74 % [58]. Another series using a transfusion trigger of 70 g/L in 18 patients with severe ARDS receiving ECMO reported survival to hospital discharge of 61 % [59]. The threshold for transfusing platelets is similarly ill defined, with recommendations varying considerably [11, 56–58, 60]. More studies are needed in order to evaluate the short- and long-term consequences of lower transfusion thresholds.

Early rehabilitation during VV-ECMO

Critically ill patients traditionally receive bed rest as part of the management. It is possible that patients develop muscle weakness even after only a few days of MV [61] that may prolong their time in ICU and in hospital and delay functional recovery resulting in slower return home and to work. Weakness and physical disability may be reduced with simple strategies of early rehabilitation in ICU, but it is unclear if it is safe during ECMO.

ECMO patients have been historically nursed with full bed rest and managed with high-level sedatives and minimal interventions. Current standard care is dominated by concerns about short-term patient safety. This short-term focus exposes patients to prolonged immobility which may be a crucial mechanism leading to muscle weakness and poorer long-term outcomes, including increased risk of mortality within the first year following ICU, and reduced health-related quality of life in survivors [62, 63].

There are no randomized controlled trials (RCTs) of rehabilitation in ECMO patients; however, there are several before–after studies and case–control studies indicating that early rehabilitation in this patient group may improve survival, reduce MV duration, reduce ICU length of stay, and improve functional recovery [64]. In one historical control study of patients receiving ECMO as a bridge to transplant, patients receiving physical training had much shorter duration of MV (4 vs. 34 days) and ICU stay (11 vs. 45 days) [18]. In an observational study of 100 ECMO patients in a specialized ECMO center in the USA, the ICU staff implemented a practice change to confirm safety and feasibility of early rehabilitation during ECMO [65]. These investigators found that 35 % (35/100 patients receiving ECMO) could participate in early mobilization and that 51 % (18/35) were able to walk. Early mobilization was considered safe and feasible when implemented with an experienced, multidisciplinary team familiar with ECMO equipment and safety procedures.

ECMO patients often have pre-existing cardiac and respiratory decline and are most likely to result in long-standing morbidity and high health care costs. Further

research is required to establish safety and efficacy of rehabilitation early in this high-risk patient group, particularly following the publication of the results of the AVERT study (RCT of very early rehabilitation following acute stroke) where the early mobilization group had worse functional recovery at 90 days [66]. Future multicenter trials are being planned to address this evidence gap.

Ethical concerns, futility, and termination of VV-ECMO

Considering the potential futility of an ECMO treatment established to treat ARF, one has to take several aspects into account. ECMO typically acts as a bridge to either recovery or to lung transplantation. Therefore, if there is neither a chance for sufficient lung recovery, in a sense that it would allow the patient to achieve sufficient gas exchange and therefore survival, nor the chance for lung transplantation, ECMO support would by definition be futile. Apart from this well-defined situation, the patient's condition, chance for a meaningful recovery, in the light of their (and/or their relatives') wishes and beliefs should provide the grounds for shared decision-making around potential futility. However, the challenges are obvious: what is an adequate window for healing? And what is the best way to demonstrate irreversibility of the lung injury making successful recovery unlikely or impossible. Importantly, many ARF patients supported with ECMO have either significant pre-existing comorbidities and/or concomitant multiorgan failure caused for example by sepsis, trauma, or other diseases. In this case, a holistic view of the patient's overall condition may better support potential futility of the treatment. Moreover, we should also consider how often recovery from ARDS might require months rather than weeks on ECMO, and therefore it is difficult to set limits to the maximum duration of the procedure.

The use of scoring systems might be helpful for judgment and decision-making. For instance, a RESP score value of lower than −6 (risk class V) indicates a probability to survive of 18 % [35]. However, considering even this low probability of survival in isolation is not enough, as there needs to be more to ECMO support than simply to prolong life—function and quality of life need to be considered as well. Therefore, the real value of these scoring systems may consist in helping to decide whether a patient should not go on ECMO, in cases when this advanced treatment option does not realistically increase the chances for survival and an acceptable outcome [67].

ECMO is an invasive, high-risk, and resource-intensive therapy that requires responsible handling of its indication and use. Medical futility represents a violation against professional medical standards, an unjustifiable utilization of resources, and an opponent to a natural process of dying [68]. With careful patient selection, the continuous re-evaluation of therapeutic goals combined with the readiness to stop ECMO therapy whenever defined and consented goals can no longer be achieved is a necessary prerequisite for clinicians and centers to recognize ECMO for what it is, i.e., a potentially life-saving tool, and not an instrument to prevent a dignified death [69].

Future directions

The rapid expansion of ECMO for adult patients with ARF [19] represents an important economic as well as technical challenge to health systems. While an area of great and often seductive promise, we currently lack the necessary evidence to support such rapid and widespread adoption. As a result, there is an urgent need for timely and rigorous evaluation of this intervention in this population of critically ill patients. However, there has been a paucity of high-quality data to help clinicians, administrators, and policy stakeholders to make informed decisions regarding the potential efficacy of ECMO in adult patients with ARF. Fortunately, clinical trials which are underway (e.g., EOLIA) or currently in development will help to better define the place for VV-ECMO in our therapeutic armamentarium for ARF. Given the time, costs, and resources needed to plan and conduct RCTs, and the small population of patients who are potentially eligible for these interventions, international cooperation and research consortia (e.g., International ECMO Network [10]) may greatly facilitate high-quality research moving forward. In addition, research evaluating important aspects of patient management during ECMO, such as optimal MV support, regional anticoagulation, and early rehabilitation, are also underway. Finally, more studies are needed regarding the long-term outcomes of these patients, as well as high-quality data regarding its cost-effectiveness and resource implications across different health systems.

As high-quality data become available from these clinical trials, they should be incorporated into evidence-based guidelines for the use of ECMO for ARF defining the optimal timing, disease characteristic, and indications for this therapy. Until then, ECMO should be considered for patients with life-threatening hypoxemia or hypercapnia refractory to conventional MV, where there is a realistic chance for a meaningful outcome, in experienced, high-volume centers.

Conclusion

Technological advances have improved the safety and simplicity of ECMO for patients with ARF and may represent an important advance in the management of these patients. Although a promising intervention, rigorous

evidence on the efficacy of ECMO in ARF is currently lacking and is needed before widespread adoption can be considered. Until then, ECMO should be considered on a case-by-case basis for patients with severe ARF failing conventional therapies and performed in referral centers with the requisite case volume and expertise.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4314-7) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
Dan Brodie is currently on the medical advisory boards of ALung Technologies and Kadence. All compensation for these activities is paid to Columbia University. Alain Combes received funding for research from Maquet Cardiovascular and is currently on the Medical Advisory Board of Xenios and Baxter. Thomas Müller received fees from Maquet for travel support to invited lectures. Antonio Pesenti received funding for research and travel from Maquet Cardiovascular and is currently on the Medical Advisory Board of Novalung and Baxter. He holds a number of patents related to CO_2 removal technology. Matthieu Schmidt received fees from Maquet for lectures. All other authors have no conflicts of interest to declare.

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