CHEST

How I Select Which Patients With ARDS Should Be Treated With Venovenous Extracorporeal Membrane Oxygenation

E. Caroline Bullen, MBBS; Ricardo Teijeiro-Paradis, MD; and Eddy Fan, MD, PhD

ARDS is a lethal form of acute respiratory failure, and because no specific treatments exist, supportive care remains the primary management strategy in these patients. Extracorporeal membrane oxygenation (ECMO) has emerged as an intervention in patients with severe ARDS to facilitate gas exchange and the delivery of more lung protective ventilation. Over the past 20 years, improvements in ECMO technology have increased its safety and transportability, making it far more available to this patient population globally. Deciding which patients with ARDS should be initiated on ECMO remains a challenging question. Numerous clinical and laboratory markers have been investigated, and multiple risk scores developed, to aid physicians in this decision-making process. However, they are still imperfect, and the choice is often based on institutional guidelines and the clinical impression of the treating physician. Given the potential risks and resource implications for this intervention, patient selection is critical and it is important to provide ECMO only to patients who have a reasonable chance for recovery or bridge to transplantation. In patients undergoing ECMO where there is no potential for recovery or transplant, the only option may be withdrawal of ECMO and palliation. These patients may be awake and interactive, which is often a very challenging scenario for patients, families, and the clinical team. In this article, we present a more controversial case and a review of the literature regarding the selection of patients with ARDS who should receive ECMO.

CHEST 2020; 158(3):1036-1045

KEY WORDS: ARDS; extracorporeal membrane oxygenation; hypoxemic respiratory failure; patient selection

Venovenous Extracorporeal Membrane Oxygenation in the Management of ARDS

ARDS accounts for about 10% of admissions to the ICU.[1] Despite significant advancements, ARDS is associated with a very high mortality—up to 45% in patients with severe disease[1,2]—and is associated with poor functional outcomes, persistent disability,[3] and a substantial economic burden.[4,5]

Advances in technology over the last 50 years have revealed venovenous extracorporeal membrane oxygenation (VV-ECMO) to be a potentially effective method to support lung function in patients with severe ARDS, allowing ultraprotective ventilation strategies

ABBREVIATIONS: $ECCO_2R$ = extracorporeal CO_2 removal; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; PEEP = positive end expiratory pressure; VILI = ventilator-induced lung injury; VV-ECMO = venovenous extracorporeal membrane oxygenation

AFFILIATIONS: From the Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON; and the Extracorporeal Life Support Program, Toronto General Hospital, Toronto, ON, Canada.

Drs Bullen and Teijeiro-Paradis contributed equally to this manuscript.

CORRESPONDENCE TO: Eddy Fan, MD, PhD, Toronto General Hospital, 585 University Ave, PMB 11-123, Toronto, ON, Canada, M5G 2N2; e-mail: eddy.fan@uhn.ca

DOI: https://doi.org/10.1016/j.chest.2020.04.016

while awaiting response to treatment.[2,6-11] Current evidence supports the use of VV-ECMO in the management of patients with severe ARDS.[2,6,7,9,12,13] Further randomized controlled trials of VV-ECMO in patients with severe ARDS are unlikely because of the challenges of trial design and recruitment, costs, and generalizability of findings into lower-volume ECMO centers.[2,14]

Because of the potential devastating complications, the impact on long-term functional outcomes, and the costs and strain on the health-care system related to ECMO deployment, appropriate patient selection is the key to its success.[15,16] Taken together, it makes drawing the line of when ECMO should or should not be offered far from straightforward.

Case Example

The patient is a 39-year-old man with no medical history, who was admitted to hospital with a 1-month history of shortness of breath, night sweats, and unexpected weight loss. CT scan demonstrated diffuse ground-glass opacities throughout both lungs, which was initially interpreted as nonresolving pneumonia. During the workup, he was diagnosed with HIV/AIDS, with a very low cluster of differentiation 4 count and HIV viral load of $>$ 61,000 copies/mL. He was found to have both *Pneumocystis jiroveci* and *Mycobacterium avium* pneumonia, and cytomegalovirus viremia. He was treated with trimethoprim/sulfamethoxazole and steroids for *P jiroveci*, azithromycin, ethambutol and rifabutin for *M avium*, and ganciclovir for cytomegalovirus.

One week after admission, he was transferred to the ICU because of acute respiratory failure requiring intubation. He continued to worsen despite deep sedation, paralysis, and optimization of mechanical ventilation. At the time of referral, his gas exchange had started to deteriorate rapidly with a pH 7.04, $Paco_2$ $>$ 115 mm Hg, and Pao_2 98 mm Hg on Fio_2 of 0.85. He was starting to require potentially injurious levels of ventilation in an attempt to improve the hypercapnic acidosis. He was subsequently initiated on VV-ECMO, and antiretroviral therapy for HIV was started.

The decision to support this patient with ECMO was in response to his young age, lack of previous medical history, single organ dysfunction at the time of presentation, and the thought that the underlying condition and immunosuppressive state was potentially reversible with treatment.

How We Do It

We encourage referring centers to optimize conventional management prior to consideration for ECMO (Fig 1). Lung protective ventilation with low tidal volumes and airway pressure, and higher levels of positive end expiratory pressure (PEEP), should be provided to all patients with moderate to severe ARDS. Failure to achieve improvements in oxygenation or ventilation should be followed by a trial of deep sedation and neuromuscular blockade and prone positioning. VV-ECMO should be considered if modest physiological targets (ie, Pao_2 55-80 and pH $>$ 7.25) are not met with these measures. ECMO should also be considered early when the intensity of mechanical ventilation is thought to be injurious (eg, sustained pre-ECMO plateau pressure $>$ 35 cm H_2O), results in hemodynamic derangements, or when low-volume ventilation results in severe acidosis (pH $<$ 7.15).

Overall, the selection process at our institution relies heavily on clinical characteristics, the expected potential for recovery, or the eligibility to bridge to transplant (Fig 1). The starting point for eligibility is the inclusion criteria from the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial.[6,17] We do not routinely use predictions scores to help with patient selection (as subsequently discussed). The presence of relative contraindications, such as older age, presence of multiorgan failure, immunosuppression, and underlying comorbidities, is the key element that may modify the decision to pursue ECMO. Prolonged time on mechanical ventilation (eg, $>$ 7 days) alone is not necessarily a criterion to turndown referrals, but we take into account the clinical trajectory over that time. For instance, we would be inclined to consider ECMO in a patient who improved for the first 5 days and then deteriorated over the next 2 to 3 days (perhaps because of new ventilator-associated pneumonia) than in a patient who continued to deteriorate steadily over the first 7 days despite optimal mechanical ventilation. The decision is shared by the attending intensivist and thoracic surgeon. If the candidate is in a remote center, the next step in the process is to decide whether to transport the patient on ECMO or mechanical ventilation. Criteria to retrieve patients on ECMO include clinical stability for transport. Cannulation is done percutaneously, with ultrasound guidance, with chest radiography and echocardiography used to confirm the appropriate position of the drainage cannula.

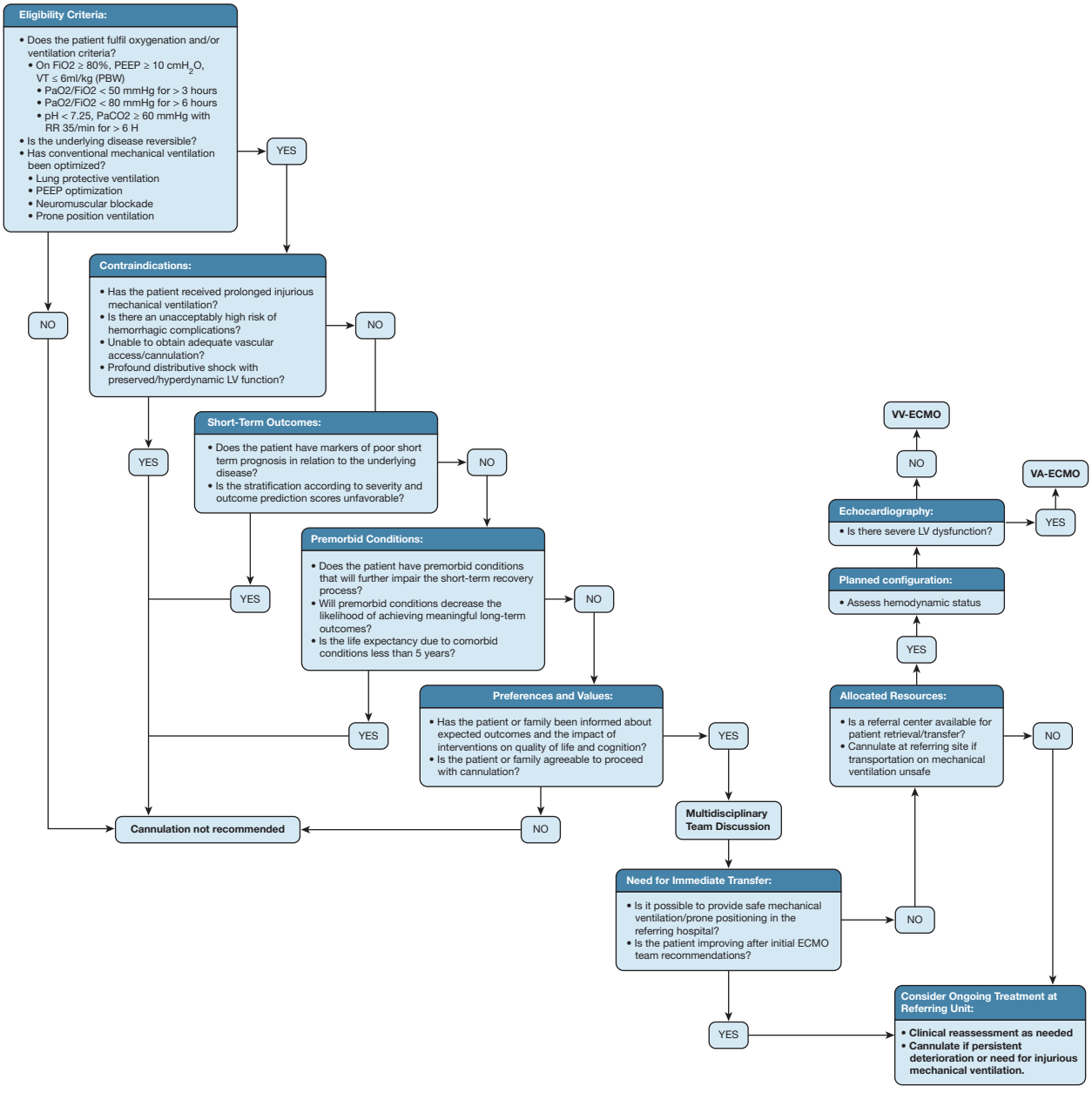

Figure 1 – *Suggested algorithm for consideration of the use of VV-ECMO in ARDS. ECMO = extracorporeal membrane oxygenation; LV = left ventricular; PBW = predicted body weight; PEEP = positive end expiratory pressure; RR = respiratory rate; VA-ECMO = venoarterial extracorporeal membrane oxygenation; VT = tidal volume; VV-ECMO = venovenous extracorporeal membrane oxygenation.*

Review of the Literature and Current Guidelines

Mechanical ventilation to maintain gas exchange is lifesaving in patients with ARDS, but can paradoxically lead to further lung injury because of a number of mechanisms known collectively as ventilator-induced lung injury (VILI).[5,18,19] The aim of VV-ECMO is to provide adequate gas exchange while allowing lung rest and to mitigate VILI. However, there are no evidence-based thresholds to guide at what point ECMO should be initiated. When VV-ECMO is considered as a bridge to recovery, reversibility of the underlying disease is key, but often difficult to define explicitly. ARDS is a systemic process which can take weeks or months to improve, and even then, meaningful long-term and functional outcomes may not be achieved.[3] The development of scoring systems and mortality prediction for patients receiving VV-ECMO has been difficult because of changes in ECMO technology over time, the relatively small and highly specific study populations, and large

TABLE 1] ECMO Indications and Contraindications From Clinical Trials and Guidelines

Study	Indications for ECMO	Contraindications
ELSO[23]	Mortality > 80%; Pao_2/Fio_2 < 80 mm Hg with Fio_2 > 90%, Murray score 3-4; CO_2 retention on mechanical ventilation despite high Pplat (>30 cm H_2O); Severe air leak syndromes; Need for intubation in patient on lung transplant list; Cardiac or respiratory collapse	Relative contraindications include mechanical ventilation at high settings for 7 d or more; major pharmacologic immunosuppression; recent or expanding CNS haemorrhage; nonrecoverable comorbidity; increasing age
Pham et al[10]	Pao_2/Fio_2 < 50 mm Hg despite PEEP 10-20 cm H_2O and Fio_2 > 80%; Pplat > 35 cm H_2O despite attempt to reduce TV to < 4 mL/kg PBW	Presence of severe comorbidities and multiorgan failure (SOFA score > 15)
Davies et al[24]	Pao_2/Fio_2 < 60 mm Hg; $Paco_2$ > 100 mm Hg with Pao_2/Fio_2 < 100 mm Hg	Irreversible CNS condition; cirrhosis with ascites, encephalopathy, or history of variceal bleeding; active and rapidly fatal malignant disease; HIV infection; weight > 120 kg; pulmonary hypertension, cardiac arrest
Patroniti et al[27]	Oxygenation index > 30; Pao_2/Fio_2 < 70 mm Hg with PEEP > 15 cm H_2O for patients already admitted to an ECMO center; pH < 7.25 for > 2 h; hemodynamic instability	Intracranial bleeding or other major contraindication to anticoagulation; previous severe disability; poor prognosis because of underlying disease; mechanical ventilation > 7 d
Peek et al[9]	Potentially reversible respiratory failure; Murray score > 3; pH < 7.2 despite optimum conventional treatment	PIP > 30 cm H_2O or Fio_2 > 80% for > 7 d; mechanical ventilation > 7 d; intracranial bleeding; contraindication to limited heparinization; contraindication to continuation of active treatment
Combes et al[6]	Pao_2/Fio_2 < 50 mm Hg with Fio_2 > 80% for > 3 h, despite optimum mechanical ventilation and adjunctive treatment; Pao_2/Fio_2 < 80 mm Hg with Fio_2 > 80% for > 6 h, despite optimum mechanical ventilation and adjunctive treatment, pH < 7.25 for > 6 h	Mechanical ventilation > 7 d; age < 18 y; pregnancy; weight > 1 kg/cm; BMI > 45 kg/m^2; chronic respiratory insufficiency treated with oxygen therapy of long duration and/or long-term respiratory assistance; history of heparin-induced thrombocytopenia; malignant disease with 5-y fatal prognosis, patient moribund; SAPS II > 90; non-drug-induced coma post-cardiac arrest; irreversible CNS pathology; decision to limit therapeutic interventions; unable to cannulate
Griffiths et al[25]	Selected adults suffering severe ARDS (lung injury score ≥ 3 or pH < 7.2 because of hypercapnia)	
Fan et al[13]	Additional evidence necessary to make definitive recommendation for or against the use of ECMO in patients with severe ARDS; consider on case by case basis	
Papazian et al[26]	Pao_2/Fio_2 < 80 mm Hg and/or when mechanical ventilation becomes dangerous; the decision to use ECMO should be evaluated early by means of contact with an expert center	

ECMO = extracorporeal membrane oxygenation; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Pplat = end-inspiratory plateau pressure; SAPS II = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.

patient heterogeneity. Therefore, VV-ECMO has often been used for rescue,[5,18] when perhaps we should be using it early when high-risk features are present,[7,15,20] and the timely correction of both life-threatening gas exchange and hemodynamics (eg, right ventricular failure) may halt the progression of organ failure. These decisions are often made on a case by case basis, but usually take into account the underlying pathophysiology (and therefore reversibility) of the lung injury,[5,18,21] any preexisting comorbidities and their physiological reserve,[22] risk vs benefit of implementing ECMO, and absence of significant contraindications.

Current Guidelines

Deciding which patients should be offered extracorporeal life support (ECLS) is still a controversial area; however, some guidelines exist (Table 1).[6,9,10,13,23-27] The Extracorporeal Life Support Organization[23] guidelines

state that VV-ECMO should be considered when the expected mortality rate surpasses 50%, and is indicated when it exceeds 80%. These recommendations likely come from historical data of using less technologically advanced interventions and late implementation as rescue therapy. Current evidence[6] has shown that earlier deployment may prevent further lung injury and organ dysfunction. The Extracorporeal Life Support Organization guidelines[23] also state that there are no absolute contraindications to ECMO. However, expert opinion[5,28,29] would consider ECMO to be contraindicated in patients with severe irreversible respiratory disease if lung transplant is not an option, or in patients with irreversible conditions unlikely to benefit from ECMO (eg, catastrophic neurologic injuries, untreatable metastatic cancer).

Patient Characteristics

The effect of age on mortality related to VV-ECMO has been investigated in multiple trials, but no absolute cutoff has been determined.[30-32] The efficacy and economic assessment of conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) trial[9] included patients < 65 years of age, but subsequent trials have been more inclusive with the EOLIA trial having no upper age limit.[6] These studies have consistently noted better outcomes in those < 45 years of age, and the worst outcomes in those > 60 to 65 years of age.[30,33] Moreover, in younger patients (< 45 years of age), ECMO should not be solely contraindicated based on organ failure because their outcomes have been shown to be better regardless of the degree of organ dysfunction.[34]

Although a raised BMI has been postulated as a relative contraindication to ECMO, several studies have suggested this is not the case, and in fact a higher BMI may be associated with improved survival.[35,36] The difficulties with ECMO in patients with obesity include vascular access, inability to achieve desired flow rates, and challenges in prone positioning either prior to, or during, ECMO.[35] Literature investigating the association between obesity and mortality on ECMO has the potential for bias because patients with very high BMI are less likely to be initiated on ECMO, and the threshold to initiate ECMO may be different because of the particular challenges of mechanical ventilation in this group of patients.[35] We do not think that morbid obesity (BMI > 40 kg/m^2) alone is a contraindication to ECMO; however, cannulation may be challenging.

Gas Exchange

The selection criteria for VV-ECMO for ARDS differs slightly between existing trials, but they have historically been based mainly on the degree of impairment of gas exchange (Table 1).[6,9,10,13,23-27] However, it should be highlighted that outcomes after VV-ECMO in ARDS are not dictated by the $Pa_{O_2}/F_{I_{O_2}}$ ratio, but by multiple other factors related to the mechanical ventilation profile and extrapulmonary organ dysfunction.[33,37,38] Blood markers which have been associated with mortality include platelet count, hemoglobin or hematocrit, fibrinogen, bilirubin, and pH.[31,39]

When VILI and hypercapnia rather than hypoxemia are the driving criteria for ECLS, the physiological rationale for implementation still relies on offloading the respiratory system by decreasing the intensity of mechanical ventilation. However, in comparison with patients who are profoundly hypoxemic, patients with VILI and hypercapnia may be managed with extracorporeal CO_2 removal ($ECCO_2R$) systems that use lower extracorporeal blood flow (ie, < 1.5 L/min).[40] Currently, there is no definitive evidence supporting the routine use of $ECCO_2R$ in patients with ARDS; however, a recent feasibility and safety study showed that $ECCO_2R$ can safely facilitate ultraprotective ventilation in ARDS.[41] A number of clinical trials exploring $ECCO_2R$ are ongoing or planned.[41-43]

Hemodynamics

During patient selection, the hemodynamic profile and other specific clinical variables should also be taken into consideration. Hemodynamic markers which have been independently associated with mortality in patients undergoing VV-ECMO include mean arterial pressure and lactate level, and norepinephrine use.[39,44]

Three common hemodynamic profiles are seen in patients with ARDS and refractory hypoxemia,[45,46] hypoxemic and vasodilated, hypoxemic with right ventricular failure, and hypoxemic with isolated left or biventricular failure. VV-ECMO can improve hemodynamics in patients with ARDS by reversing hypoxemia and acidosis, while decreasing the intensity of mechanical ventilation, therefore reducing intrathoracic pressures, reducing the need for deep sedation, and improving right ventricular function. In patients who are hemodynamically unstable and requiring high levels of vasoactive support, we routinely perform echocardiography during the initial assessment to guide the ECMO team in choosing the most

appropriate circuit configuration (VV-ECMO vs venoarterial ECMO) (Fig 1).

Risk Prediction Scores

As a result of the difficult nature of patient selection for VV-ECMO in ARDS, a number of risk prediction scores have been trialed and developed to aid ECMO teams to select the candidates in whom VV-ECMO is likely to be of benefit (Table 2).[31,32,34,36,44] The most common factors throughout these scores which worsen prognosis appear to be older age, longer duration of hospital stay or mechanical ventilation before ECMO initiation, and an immunocompromised state. The Murray score—which concentrates only on the respiratory system and mechanical ventilation profile—is also used by some institutions for ECMO consideration (Table 1).[47]

In these studies, looking at risk scores for VV-ECMO in ARDS, ventilatory parameters that were associated with higher mortality included higher pre-ECMO plateau pressure, lower pre-ECMO PEEP, higher peak inspiratory pressure and $Paco_2$, and number of days of pre-ECMO mechanical ventilation.[32,36] There appears to be a time point specifically at 7 days of mechanical ventilation where there is a reduction in survival,[32] and also a potential beneficial impact of early use of ECMO (< 48 h). This suggests we should perhaps adopt a different approach to initiation of ECMO at earlier stages of ARDS rather than as a rescue therapy.[6,20,32]

Other factors associated with improved outcomes include viral and primary pulmonary infections (particularly H1N1), aspiration pneumonia, and adoption of standard of care treatments such as prone

TABLE 2] Prognostic Scoring Systems for Patients Supported With ECMO for Acute Respiratory Failure

Study	Factors That Worsen Prognosis	Factors That Improve Prognosis
Pappalardo et al[44] (N = 60)	Increased length of hospital stay pre-ECMO Increased creatinine Increased bilirubin Lower MAP Lower haematocrit	
Schmidt et al[36] (N = 140)	Age Immunocompromise Length of mechanical ventilation before ECMO > 6 d Pplat > 30 cm H_2O PEEP < 10 cm H_2O Higher SOFA score	Prone positioning pre-ECMO Higher BMI
Roch et al[34] (N = 85)	Higher age Higher SOFA score	Influenza pneumonia
Enger et al[39] (N = 304)	Increased age Immunocompromise Minute ventilation Low pre-ECMO hemoglobin High day 1 Fio_2 High day 1 norepinephrine dose Low day 1 fibrinogen	High day 1 CRP
Schmidt et al[32] (N = 2,355)	Increasing age Immunocompromise Increased length of mechanical ventilation prior to ECMO Extrapulmonary infection Higher peak inspiratory pressure Neurologic dysfunction Bicarbonate (HCO_3^-) infusion pre-ECMO Higher $Paco_2$ Nitric oxide use pre ECMO Cardiac arrest	Neuromuscular blockade Asthma Aspiration pneumonitis
Hilder et al[31] (N = 108)	Longer length of hospital stay before ECMO Lower MAP Higher lactate Lower pH Lower platelet concentration	

CRP = C-reactive protein; MAP = mean arterial pressure. See Table 1 legend for expansion of other abbreviations.

positioning and neuromuscular blockade.[27,31,32,36] Considering the present case, it is worth expanding on immunocompromised status because it is considered in all aforementioned scoring systems to be associated with worse outcomes. Extremely poor outcomes have been seen in patients who receive ECMO for acute respiratory failure post-stem cell or bone marrow transplant, with survival rates of < 20%.[48] There is a paucity of data regarding ECMO in patients with HIV, but it should perhaps be placed in a different category because of its potential reversibility with appropriate antiretroviral therapy, resulting in more favorable outcomes.[49]

Although prediction scores may help standardize patient selection and provide insights into expected outcomes of the intervention, these prediction scores have caveats, mostly related to external validation and lack of insight into long-term outcomes which have limited their use.[50] Also, because the patient population used to develop these scores all received ECMO, they are unlikely to help us identify all patients who may benefit from this therapy. Risk scoring systems perhaps can be most useful in identifying those who have very high predicted mortality even if they receive VV-ECMO.[51] For these reasons, we do not use these scoring systems routinely when considering patients for VV-ECMO. However, they can be useful to reassure physicians and family members regarding the reason for declining high-risk patients for ECMO.

A Bridge to Nowhere: Futility on VV-ECMO

When VV-ECMO is considered as a bridge to recovery, reversibility of the underlying disease is key, but often difficult to define explicitly. ARDS is a systemic process which can take weeks or months to improve, and even then, meaningful long-term and functional outcomes may not be achieved.[3] Setting that limit of when instituting VV-ECMO would be futile is challenging and is very difficult to predict. The determination of futility is often made by expert opinion and individual center preferences. It is usually based on the presence of specific clinical factors that indicate the patient has passed the point of recovery based on their hemodynamics, mechanical ventilation profile, or perceived physiological reserve.[5,15,18,22]

In this tenor, it might be helpful to take into consideration clinical scenarios where ECMO is unlikely to be successful, such as in patients with ARDS and refractory septic shock with normal (or hyperdynamic) biventricular function.[52] In patients with severe vasodilatory shock that is unresponsive to multiple vasopressors, VV-ECMO will be ineffective in providing enough flow through the oxygenator to reverse the hypoxemia. In this situation, venoarterial ECMO may also be insufficient in providing the hemodynamic support because the ventricular function is often hyperdynamic, and vasodilation is not modified by ECLS.[52,53]

Additional circumstances where we do not offer ECMO include the following: chronic respiratory disease with no hope of recovery or transplant, recent allogenic stem cell transplantation, and ARDS with advanced multiorgan failure.

Patient Goals, Preferences, and Outcomes

It has been shown that the impact of critical illness on functional outcomes, particularly after ARDS, is significant.[3,33] Patients with ARDS (and their families) should be fully informed about the impact ECLS may have on their health-related quality of life and cognition. This may help align outcome expectations with each individual patient's preferences. It has been shown that patients who survived VV-ECMO for ARDS have greater decrements in health-related quality of life than patients who survived ARDS only supported with mechanical ventilation.[54] Interestingly, patients treated with ECMO were found to have less psychological morbidity, including depression and anxiety.[54] Pulmonary and functional capacity was found to be similar between the two groups,[33,54] as were cognitive outcomes even after adjusting for worse oxygenation and education level.[55] Overall, around 50% of these survivors returned to work, with only 50% of those returning to their previous role.[54,55]

ECMO Center/System Considerations

Evidence has shown improved outcomes when patients are transferred to high-volume respiratory failure centers, where multidisciplinary teams are able to provide specialist care to these complex patients[22,56] with enough resources for prolonged ECMO runs and long-term support after ECMO.[16] This requires an established communication network, health-care policies, and infrastructure, and the capacity to deploy retrieval teams to guarantee safe patient transport on or off VV-ECMO. Low-volume centers are more likely to start VV-ECMO for ARDS at a later stage, as salvage therapy, because there are proportionally higher risks of iatrogenic complications related to the cannulation process and the ECMO circuit.[37] Physicians may opt not to proceed with cannulation under these circumstances

with a higher risk profile and potentially higher mortality.

To further portray just how challenging the existing decision process is for selecting which patients should be managed with VV-ECMO, evidence has shown that 6-month survival of patients with ARDS declined for a VV-ECMO referral is around 16% in the United Kingdom.[22] The 6-month survival of patients managed locally at the referring hospital with active ECLS specialist consultation support is 71%.[22] This means that almost one-third of the patients accepted for a VV-ECMO referral who were thought to be safe to manage at their local hospital in conjunction with the ECMO specialists' recommendations still died, whereas 16% of those deemed too sick to benefit from VV-ECMO survived. This potentially implies two things: (1) there is an underestimation of survival based on the clinical picture and severity indexes for patients declined for ECMO referral, and (2) we are perhaps overestimating survival or misunderstanding the disease process in those accepted for referral. Deciding who should receive ECMO is a fine balance of risk vs benefit, and our ability to decide what tips that balance is still imperfect.

Summary of the Approach to the Question

Overall, the decision to support patients with ARDS with VV-ECMO remains extremely challenging. Intensivists receiving ECMO referrals should not put on themselves the full responsibility of individually making decisions regarding patient appropriateness. This decision should be a shared process among the whole ECMO team including surgeons, intensivists, physicians, and perfusionists, in conjunction with the patient or their substitute decision-maker. Although still imperfect, the decision-making process should be based on the presence of strong clinical criteria, the possibility of organ and functional recovery, the lack of improvement after optimization of mechanical ventilation, and the existence of a social network to allow for rehabilitation and aftercare. Cannulation should not be considered when risks exceed benefits, when significant extrapulmonary organ failure has ensued, when stratification indexes identify patients with very poor short-term outcomes or very high mortality, and when there is no possibility of providing prolonged high-quality care because of the lack of resources and expertise. Figure 1 demonstrates our suggested algorithm to guide which patients should be considered for ECMO.

In our institution, we receive ECMO referrals for many indications from a large geographic area. We have discussed a case here which may be considered controversial to some, but we hope to demonstrate the need to keep an open mind when considering patients for ECMO and to put together a complete clinical picture. Although the present patient was immunocompromised, he is young and prior to this presentation a healthy patient with no other comorbidities. He presented with a potentially reversible cause of lung injury in the context of single organ dysfunction. In these settings, like with other interventions in the ICU, it may be most appropriate to give a time-limited trial of ECMO, accepting the risk of potentially having to withdraw this therapy, after a fulsome discussion with the patient and/or their surrogates. This is perhaps the only way we will start to understand the full potential for ECMO in ARDS.

Acknowledgments

Financial/nonfinancial disclosures: E. F. is supported by a New Investigator Award from the Canadian Institutes of Health Research and reports receiving personal fees from ALung Technologies, Abbott, and MC3 Cardiopulmonary, outside the submitted work. None declared (E. C. B., R. T.-P.).

References

1. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.
2. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172.
3. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
4. Barrett KA, Hawkins N, Fan E. Economic evaluation of venovenous extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Crit Care Med*. 2019;47(2):186-193.
5. Brodie D, Slutsky AS, Combes A. Extracorporeal life support for adults with respiratory failure and related indications: a review. *JAMA*. 2019;322(6):557-568.
6. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378(21):1965-1975.
7. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc bayesian analysis of a randomized clinical trial. *JAMA*. 2018;320(21):2251-2259.
8. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-1668.
9. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363.

10. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285.
11. Aoyama H, Uchida K, Aoyama K, et al. Assessment of therapeutic interventions and lung protective ventilation in patients with moderate to severe acute respiratory distress syndrome: a systematic review and network meta-analysis. *JAMA Netw Open*. 2019;2(7):e198116.
12. Bartlett RH. Extracorporeal membrane oxygenation for acute respiratory distress syndrome: EOLIA and beyond. *Crit Care Med*. 2019;47(1):114-117.
13. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195:1253-1263.
14. Gattinoni L, Vasques F, Quintel M. Use of ECMO in ARDS: Does the EOLIA trial really help? *Crit Care*. 2018;22(1):171.
15. Cavayas YA, Thakore A, Fan E. Extracorporeal strategies in acute respiratory distress syndrome. *Semin Respir Crit Care Med*. 2019;40(1):114-128.
16. MacLaren G. When to initiate ECMO with low likelihood of success. *Crit Care*. 2018;22(1):217.
17. Abrams D, Ferguson ND, Brochard L, et al. ECMO for ARDS: From salvage to standard of care? *Lancet Respir Med*. 2019;7(2):108-110.
18. Del Sorbo L, Cypel M, Fan E. Extracorporeal life support for adults with severe acute respiratory failure. *Lancet Respir Med*. 2014;2(2):154-164.
19. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126-2136.
20. Combes A, Brechot N, Luyt CE, Schmidt M. Extracorporeal membrane oxygenation: Beyond rescue therapy for acute respiratory distress syndrome? *Curr Opin Crit Care*. 2017;23(1):60-65.
21. Agerstrand CL, Bacchetta MD, Brodie D. ECMO for adult respiratory failure: current use and evolving applications. *ASAIO J*. 2014;60(3):255-262.
22. Gillon SA, Rowland K, Shankar-Hari M, et al. Acceptance and transfer to a regional severe respiratory failure and veno-venous extracorporeal membrane oxygenation (ECMO) service: predictors and outcomes. *Anaesthesia*. 2018;73(2):177-186.
23. Extracorporeal Life Support Organization (ELSO). ELSO guidelines for cardiopulmonary extracorporeal life support, Version 1.4 August 2017. Ann Arbor, MI. www.elso.org. Accessed June 14, 2020.
24. Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302(17):1888-1895.
25. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res*. 2019;6(1):e000420.
26. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann Intensive Care*. 2019;9(1):69.
27. Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A(H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive Care Med*. 2011;37(9):1447-1457.
28. Abrams D, Brodie D. Extracorporeal membrane oxygenation for adult respiratory failure: 2017 update. *Chest*. 2017;152(3):639-649.
29. Fan E, Gattinoni L, Combes A, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory failure: a clinical review from an international group of experts. *Intensive Care Med*. 2016;42(5):712-724.
30. Deatrick KB, Mazzeffi MA, Galvagno SM, et al. Outcomes of venovenous extracorporeal membrane oxygenation when stratified by age: How old is too old? *ASAIO J*. 2020;66(8):946-951.
31. Hilder M, Herbstreit F, Adamzik M, et al. Comparison of mortality prediction models in acute respiratory distress syndrome undergoing extracorporeal membrane oxygenation and development of a novel prediction score: the PREdiction of Survival on ECMO Therapy-Score (PRESET-Score). *Crit Care*. 2017;21(1):301.
32. Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med*. 2014;189(11):1374-1382.
33. Enger TB, Philipp A, Lubnow M, et al. Long-term survival in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation. *Crit Care Med*. 2017;45(10):1718-1725.
34. Roch A, Hraiech S, Masson E, et al. Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. *Intensive Care Med*. 2014;40(1):74-83.
35. Galvagno SM, Pelekhaty S, Cornachione CR, et al. Does weight matter? Outcomes in adult patients on venovenous extracorporeal membrane oxygenation when stratified by obesity class [published online ahead of print October 28, 2019]. *Anesth Analg*. https://doi.org/10.1213/ANE.0000000000004454.
36. Schmidt M, Zogheib E, Rozé H, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Med*. 2013;39(10):1704-1713.
37. Ahuja A, Shekar K. Patient selection for VV ECMO: Have we found the crystal ball? *J Thorac Dis*. 2018;10(suppl 17):S1979-S1981.
38. Pappalardo F, Crivellari M. Predicting outcome of venovenous ECMO: Look outside the lung! *J Thorac Dis*. 2018;10(3):1356-1360.
39. Enger T, Philipp A, Videm V, et al. Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: a prospective observational study. *Crit Care*. 2014;18(2):R67.
40. Morelli A, Del Sorbo L, Pesenti A, Ranieri VM, Fan E. Extracorporeal carbon dioxide removal (ECCO 2 R) in patients with acute respiratory failure. *Intensive Care Med*. 2017;43(4):519-530.
41. Combes A, Fanelli V, Pham T, Ranieri VM. Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. *Intensive Care Med*. 2019;45(5):592-600.
42. Fitzgerald M, Millar J, Blackwood B, et al. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care*. 2014;18(3):222.
43. McNamee JJ, Gillies MA, Barrett NA, et al. pRotective vEntilation with veno-venouS lung assisT in respiratory failure: a protocol for a multicentre randomised controlled trial of extracorporeal carbon dioxide removal in patients with acute hypoxaemic respiratory failure. *J Intensive Care Soc*. 2017;18(2):159-169.
44. Pappalardo F, Pieri M, Greco T, et al. Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. *Intensive Care Med*. 2013;39(2):275-281.
45. Del Sorbo L, Fan E. Indications and contraindications in adults with respiratory failure. In: Borgan TV, ed. *Extracorporeal Life Support: The ELSO Red BooK*. Ann Arbor, MI: Extracorporeal Life Support Organization; 2017:415-428.
46. Doufle G, Roscoe A, Billia F, Fan E. Echocardiography for adult patients supported with extracorporeal membrane oxygenation. *Crit Care*. 2015;19:326.
47. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis*. 1988;138(3):720-723.
48. Wohlfarth P, Ullrich R, Staudinger T, et al. Extracorporeal membrane oxygenation in adult patients with hematologic malignancies and severe acute respiratory failure. *Crit Care*. 2014;18(1):R20.
49. Rilinger J, Staudacher DL, Rieg S, Duerschmied D, Bode C, Wengenmayer T. Extracorporeal membrane oxygenation in Pneumocystis jirovecii pneumonia: outcome in HIV and non-HIV patients. *Crit Care*. 2019;23(1):356.

50. Brunet J, Valette X, Buklas D, et al. Predicting survival after extracorporeal membrane oxygenation for ARDS: an external validation of RESP and PRESERVE scores. *Respir Care*. 2017;62(7):912-919.

51. Fan E, Pham T. Extracorporeal membrane oxygenation for severe acute respiratory failure: Yes we can! (But should we?). *Am J Respir Crit Care Med*. 2014;189(11):1293-1295.

52. Schmidt M, Brechot N, Combes A. Ten situations in which ECMO is unlikely to be successful. *Intensive Care Med*. 2016;42(5):750-752.

53. Brechot N, Luyt CE, Schmidt M, et al. Venoarterial extracorporeal membrane oxygenation support for refractory cardiovascular dysfunction during severe bacterial septic shock. *Crit Care Med*. 2013;41(7):1616-1626.

54. Wilcox ME, Jaramillo-Rocha V, Hodgson C, Taglione MS, Ferguson ND, Fan E. Long-term quality of life after extracorporeal membrane oxygenation in ARDS survivors: systematic review and meta-analysis. *J Intensive Care Med*. 2020;35(3):233-243.

55. Sylvestre A, Adda M, Maltese F, et al. Long-term neurocognitive outcome is not worsened by of the use of venovenous ECMO in severe ARDS patients. *Ann Intensive Care*. 2019;9(1):82.

56. Barbaro RP, Odetola FO, Kidwell KM, et al. Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med*. 2015;191(8):894-901.