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REVIEW ARTICLE

Finding the needle in haystack of questions: ECMO in hypoxemic respiratory failure.

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ABSTRACT

Extracorporeal membrane oxygenation (ECMO) has gained significant attraction as a supportive measure for severe cardio-respiratory failure over the past decade and a half. Despite advances in the management of acute respiratory distress syndrome (ARDS) and its associated respiratory failure, there remain challenges for researchers and clinicians. Lung-protective mechanical ventilation and fluid restriction are widely accepted strategies for ARDS care. However, the precise role of ECMO in managing ARDS patients remains to be clearly defined. ECMO offers a potential solution for the hypoxemia and hypercapnia that arise from respiratory failure through its extracorporeal principles. Recent technological advancements have contributed to the widespread use of ECMO in critical care medicine. Nevertheless, several questions regarding its optimal application persist, with patient-centered outcomes at the forefront of care delivery. The discussion regarding the details of physiological principle underlying ECMO, various cannulation strategies, and monitoring approaches is beyond the scope of this review. In this article, we aim to provide valuable insights and address relevant queries pertaining to the optimal use of ECMO in critical care medicine.

Keywords: *ARDS, ECMO, extracorporeal membrane oxygenation, hypoxemia, respiratory failure.*

INTRODUCTION

The clinical entity acute respiratory distress syndrome (ARDS), the most common form of severe hypoxemic respiratory failure encountered in hospitalized patients, is familiar to physicians since its 1967 publication.[1] It remains an underdiagnosed and underappreciated condition. Pneumonia, sepsis, and aspiration are the three main culprits responsible for the development of ARDS. This syndrome in its severe form is associated with 50% mortality among patients with the diagnosis. This stems mainly from the lack of definitive treatment despite years of translational and clinical research focusing on its pathophysiology.[2] The recently concluded COVID-19 pandemic leading to millions of deaths across the globe is a striking example of the devastation that can be attributed to ARDS. The major burden of the COVID-19 disease process was shared by the lungs ultimately leading to the dreaded complication of, ARDS.3 To date, prevention such as vaccination for COVID-19, aspiration precautions, and treatment of inciting events such as appropriate early antimicrobials for pneumonia remain the primary focus in the care of ARDS patients.[1-3] Respiratory support with mechanical ventilators is considered the savior in the care of severely affected patients with hypoxemia. However, there are many unfortunate patients who cannot be salvaged by the available mechanical ventilator strategies.

Extracorporeal membrane oxygenation (ECMO) is considered a rescue strategy for patients with severe ARDS.[4] ECMO as a support system in the management of severely ill patients with ARDS has not been widely accepted.[5] The main reason is the lack of strong scientific data in support of its use. After the publication of the CESAR trial and the H1N1 pandemic in 2009, the use of ECMO across the globe has significantly increased. More recent EOLIA trials and the benefits of ECMO during the COVID-19 pandemic have certainly improved the number of believers in ECMO support.[6-8] There are many myths about the role of ECMO in the care of severe cardio-respiratory failure. Without a doubt, ECMO support opens the door to education and research for its wider application to benefit patients in need. We will outline some of the established facts and the challenges concerning using ECMO for hypoxemic respiratory failure.

What is ECMO?

ECMO stands for extracorporeal membrane oxygenation and is a type of miniature cardiac bypass machine used in the operation theater for cardiac surgeries. The external membrane lungs take over the oxygenation and ventilation process of native lungs. This is achieved at the bedside by drainage of deoxygenated blood from the patient by a large cannula placed in the peripheral veins and then return of the oxygenated blood via another cannula to the right side of the heart. There are two main types of ECMO support: veno-venous ECMO (VV-ECMO) and veno-arterial ECMO (VA-ECMO). VV-ECMO is intended for respiratory support and requires a functionally normal heart to deliver oxygenated blood to distant organs. VA-ECMO bypasses the functions of the heart and lungs and helps in both circulation and the oxygenation/ventilation process. VA-ECMO is more complex than the VV-ECMO, both in terms of initiation and daily management, as well as associated with more complications.[4]

Who benefits from ECMO?

It is a difficult question to answer given the lack of robust scientific data;[5] however, it is important to have the answer for a successful outcome. Mortality of ARDS patients on ventilatory support remains high irrespective of the inciting event. This has remained true during the influenza and COVID-19 pandemic. Every single passing day brings a plethora of knowledge about the etiopathogenesis and treatment strategies of ARDS for the community to assimilate and apply at the bedside. Looking for a single definitive answer is probably a futile approach. Rather, we should be open to the concept of a "goal congruent and shared decision approach" to patient care. While the care team provides the best available care at their disposal, the alternative should also be explored simultaneously. The true contraindications for ECMO support have become a moving target. The reasons are mainly due to the mounting of clinical experiences over the last decades and technological advancements. ECMO should be considered at the earliest encounter of hypoxemic respiratory failure in a hospitalized patient.[9] The recently published ESICM guidelines are a testament to the benefits of ECMO in hypoxemia.[10]

How to determine the feasibility of ECMO?

ECMO is resource intensive and limited to a handful of centers around the world.[11] Its application in ARDS management is no longer considered optional but rather a required intervention. However, socioeconomic evaluation prior to cannulation is essential for sparse resource distribution and benefits. Timely discussion about the need and the goals of ECMO support is important to maximize the benefits. Allowing ECMO to run until the lungs can recover remains the best goal. However, it can also be instituted as a bridge to decision-making and/or transplantation. The important precautionary step is to avoid the situation called "a bridge to nowhere" at best. While it is feasible to provide ECMO in all patients, it is more important to know the exit strategies at the outset because ECMO practice has been limited to the brick-and-mortar area of the hospital until now.

Which modalities to use?

The most common clinical manifestation of ARDS is acute hypoxemic respiratory failure. The ECMO modality or configuration which has been beneficial for refractory hypoxemic patients is called VV-ECMO.[11] The logical conclusion of considering VV-ECMO for hypoxemic patients is marred by controversy, mainly concerning refractory hypoxemia. While it is feasible to support the patient in all

spectrums of hypoxemia as defined by the P/F ratio, the best cutoff to reap the maximum benefits remains to be proven. Suboptimal cardiac function necessitates the application of veno-arterial (VA-ECMO) to allow both the heart and lungs to rest. The existing literature with respect to the use of ECCO2R (extracorporeal carbon dioxide removal) in ARDS is not conclusive enough to use at the bedside.[4,11]

How and where to cannulate the patients?

Technological advancement in the design and adaptation of innovative cannulation strategies over the years has solved many hurdles of ECMO implementation at the bedside. The place, person, and practice of cannulation should be tailored to local expertise and individual patient needs. Firsthand information about vasculature and the use of ultrasonography during the initiation process avoids surprises during cannulation.[4,11] Commonly applied strategies for VV-ECMO support include femoral vein drainage and internal jugular return cannulation, and vice-versa. Dual lumen single internal jugular cannulation strategies are fading after their initial widespread applications for logistical issues, particularly recirculation due to dislodgements. Nevertheless, it does provide excellent patient comfort for long-term and mobile ECMO support.

What anticoagulation strategies and monitoring goals should be used?

The feasibility of a smooth functioning extracorporeal circuit entails the need for anticoagulation. While bleeding remains the most feared complication related to ECMO support, there are also reports of both symptomatic and asymptomatic thrombotic events. The etiopathogenesis, ideal therapeutic agents, and armamentariums to prevent bleeding and clotting remain intense areas of research.[12,13] The circuit's tubing is heparin-coated, though its role in the prevention of clotting remains questionable. Heparin has been the time-tested agent and is still the most frequently used anticoagulant by many centers. However, bivalirudin is getting an edge over heparin, given its favorable pharmacologic properties, and reported benefits with respect to incidence of thrombocytopenia, circuit component changes, and patient outcomes.[14] Contraindications to anticoagulation in a patient under consideration for ECMO support need special attention, as the existing circuit components as well as the membranes cannot function optimally without it in the long run.

How do you wean and discontinue the support?

Well-validated and universally accepted practice guidelines for ECMO weaning and discontinuation are not available, though its need is well perceived by practitioners given the inherent risk of ECMO support, as well as the resource-intensive nature of the procedure. Standardized ECMO weaning parameters would be helpful to avoid the risk of complications, reduce cost, and ensure equitable resource utilization. Weaning should be considered as soon as the primary pathology for which the ECMO support is called into action is resolved or improved.[11] The simplest way to test the weaning readiness is to discontinue the sweep gas flow in VV-ECMO support and monitor the patient's hemodynamics. The alternative is gradually lowering the ECMO blood flow. It is important to have acceptable safety margins e.g., PEEP, FIO2, and power in the mechanical ventilatory (MV) settings to manage the patient off ECMO support.[11,15] Irrespective of the path chosen, it is important to discuss the need for repeated ECMO runs and reaffirm the goals with the patient, family, and care team to avoid confusion and discomfort.

What exit strategies to follow?

The boundaries of ECMO utilization are limited. Exploring the existing strategies at the outset of the clinical application is essential. The goals of ECMO use are split into three broad types: support through recovery, bridge to transplant, and support until destination/death. The purpose of knowing the goals before initiation is to provide medically and ethically appropriate care to the patient.[4,11] It will also help to prevent conflict between the care providers and family members.

How to solve the ethical dilemmas?

Multiple ethical issues come to the surface when the disease process is deemed lethal, and there is an equipoise of benefits on the interventions.[16] The pandemic forced society and its governing system to adopt novel approaches for resource allocation to deal with constraints in the care process. When it comes to the practice of ECMO, the first important ethical dilemma is to decide the clinical scenarios for obligatory and expanded support. The next one is the decision for discontinuation of therapy in non-recovering and non-transplantable patients. Interventions including ECMO to rescue patients from severe cardiorespiratory failure should be aligned with the patient's goal. We should pause to apply the "Do Everything" recipe of modern medical practice. Also, consideration for mandatory ethics team involvement before or immediately after ECMO initiation is probably the best preventative approach to avoid subsequent dilemmas.[17]

Table 1. Recent Evidences for use of ECMO in ARDS.

Name and Year of Publication	Type of Study	Number of Patients	Type of Patients	Primary Outcome	Limitations
[18]ANZ-ECMO study 2009	Observational	68	Confirmed or suspected cases of 2009 influenza A(H1N1)–related respiratory disease Age: <65 Years	*Mortality rate:* 21% (95% CI, 11%-30%)	Case Series
[6]CESAR Study 2009	Single Center Rrandomised controlled trial	180 (90 ECMO vs 90 Conventional)	- Age: 18–65 years -Murray score >3·0 or pH <7·20 - Reversible respiratory failure	*Survival without disability at 6 months* 63% vs 47% (RR 0·69; 95% CI 0·05–0·97, p=0·03)	Absence of standardised treatment protocols
[19]The UK H1N1 ECMO registry 2011	Propensity Matched Cohort Study	75	Adults with suspected or confirmed H1N1-associated respiratory failure	*Hospital mortality rate* for ECMO-referred vs non–ECMO-referred patients: 24.0% vs 46.7% (RR, 0.51 [95% CI, 0.31-0.84]; P=.008)	Lack of standardized protocol for patient management and referrals
[20]French REVA H1N1 Registry Study 2013	Propensity Matched Cohort Study	123	Adults H1N1-associated ARDS	*ICU mortality :* Non-ECMO 22% vs. ECMO 50%; P < 0.01)	Missing data and lack of standardized patient management protocols
[7]EOLIA 2018	Multi Center Rrandomised controlled trial	249 (124 ECMO vs 125 Control)	Adult intubated ARDS, on MV @ FIO2>80%, tidal volume (VT) 6 ml per kg, (PEEP) >10 cm of water for <7 days, and • P/F <50 mmHg for >3 hours • P/F <80 mmHg for >6 hours despite MV optimization and adjunctive therapies. • Arterial blood pH <7.2 and PaCO2 >60 mmHg for >6 hours despite MV adjustment to Pplat ≤32 cm H2O & PEEP <8	*Mortality at 60 days:* 35% vs 46% (RR, 0.76 [95% CI, 0.55 - 1.04]; P=0.09)	Premature stoppage of trials and crossover between treatment arms
[21]ECMO in COVID19 2022	Systematic Review and Meta-analysis	4044	Adult COVID-19 patients received VV ECMO	*Overall mortality rate:* 39%	Heterogeneity in subjects, outcome definitions and incomplete data.

CONCLUSION

ECMO is the most promising yet disruptive intervention in patients with severe cardio-respiratory failure. The patient population that can derive optimal benefits from ECMO support and the most effective strategies for implementing this technology at the bedside have yet to be clearly defined. Believers favor early use once the conventional, evidenced-based strategies including low tidal volume ventilation, paralytics, pulmonary vasodilators, and proning are deemed futile. Although less-than-perfect, there are numerous studies in the literature and anecdotal success stories to support this ideology. Table 1 provides a comprehensive overview of the evidence supporting the use of ECMO in acute respiratory distress syndrome (ARDS). On the other hand, disbelievers want to wait until the maximum therapeutic interventions have been exhausted. Arguments cite a lack of well-conducted studies, the resource-intensive (amplified during the pandemic) nature of the practice, and the multitude of ethical dilemmas ECMO brings to the forefront. We, as physicians at the bedside are intrigued by many questions and try to find the best possible answers to attest or refute our belief on the application of ECMO in ARDS. The most important part of this process is deciding the candidacy for support, and the need to individualize patient care needs.

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