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REVIEW ARTICLE

Extracorporeal Membrane Oxygenation in Respiratory Diseases in Adults

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Abstract

Extracorporeal membrane oxygenation (ECMO) was first used in adults in 1972 in a young patient with post-traumatic acute respiratory distress syndrome (ARDS). The technology is derived from the cardiopulmonary bypass machine used for cardiac surgery, modified for a longer-term support of respiratory and/or cardiac function. There are two major types of support that may be provided with ECMO, veno-venous ECMO (VV-ECMO) and veno- arterial ECMO (VA-ECMO). The former is used in patients with good cardiac function, in an effort to support lung function, while the latter is used in patients with poor cardiac function, in an effort to support the failing heart. Significant advances continue to be made in the field of extracorporeal life support (ECLS) and the modality promises to supplement the management options available for the niche role in management of patients with severe cardiac and respiratory disease. In this review, we discuss the latest developments and usage of ECMO in respiratory diseases in adults.

Key words

Extracorporeal membrane oxygenation, respiratory diseases, adults

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Introduction

Extracorporeal membrane oxygenation was first used in adults in 1972 in a young patient with post-traumatic acute respiratory disease syndrome (ARDS) [1]. The technology arose from cardiopulmonary bypass machine used for cardiac surgery but modified for longer-term support of respiratory and/or cardiac function. Its initial progress was plagued by various complications that ranged from finding the compatible pump mechanisms, to hemolysis, to blood clotting within the tubing, to finding a suitable method of oxygenation of the extracted blood.

Most of the complications were related to the oxygenators. Initially used oxygenators were the simple, less expensive bubble oxygenators where blood is exposed directly to gas. The direct blood-gas interface caused blood trauma and protein degradation, leading to hemolysis, platelet destruction, and microemboli [2, 3]. These systems were eventually replaced with membrane oxygenators, where the blood is separated from gas by a semi-permeable membrane, mimicking human lung and fewer complications [4, 5, 6]. This was a major step in advancement of the technology and with the subsequent improvement in membrane material facilitated safer extracorporeal oxygenation for prolonged period of time

A large randomized controlled trial [7] conducted in 1974 did not show significant difference in mortality between ECMO versus conventionally treated adult ARDS patients and dampened the initial enthusiasm about ECMO. Technology advances and the 2009 H1N1 influenza pandemic spurred the interest on ECMO as a rescue therapy, especially for young patients with ARDS who were failing conventional therapy [8]. This review article is aimed to familiarize readers about ECMO, its indications, its utility, possible complications, and gives a glimpse of possible future directions of care especially in pulmonary disease.

Overview

ECMO refers to the process of long-term extracorporeal support for oxygenation while the failing heart or lung rejuvenates. This is achieved by draining deoxygenated blood via a cannula to an external circuit of primed tubing to a membrane oxygenator which oxygenates the blood and a centrifugal pump which returns the oxygenated blood back into the circulation. Although there are various other components in the circuit, the main ones are the oxygenator and the pump. Typically, the blood flow through the circuit is at the rate of 100ml/kg/minute and requires placement of large bore cannulas, usually 21-24 French for adults. Another significant fact is that CO_2 removal is more efficient than oxygenation because of the solubility and diffusion properties of CO_2 relative to O_2

There are two major types of support that may be provided with ECMO (Table 1), Veno-venous ECMO (VV-ECMO) and veno- arterial ECMO (VA-ECMO).

VV-ECMO

In VV- ECMO, blood is extracted from a large vein into the ECMO circuit where gas exchange takes place. The oxygenated blood is then pumped back into the venous system, which then passes through the right atrium, and the patient's heart pumps the oxygenated blood through the pulmonary and then to the systemic circulation. As it requires the patient's native heart to pump the blood through the circuit, VV-ECMO can be used only in patients with good cardiac function to support the lungs. It does not provide support to maintain cardiac output.

Vessel cannulation may be done in several ways, ranging from a femoral-jugular approach, to a bi-femoral setting, or to a single bicaval double lumen cannula. The oxygenated blood from ECMO mixes with the deoxygenated blood in the right atrium. The systemic oxygen tension will be low and will depend on the cardiac output and the hemoglobin concentration of the patient. One of the major technical problems in VV-ECMO is recirculation. As the oxygenated blood from the circuit is sent back to a vein, some of the oxygenated blood can directly go back to the draining cannula without going to the systemic circulation. A 30% recirculation is generally considered

Table 1. **Types of ECMO**

	VV- ECMO	VA-ECMO
Cannulation type	— Blood drained from vein and returned to vein Vein: jugular-femoral, right atrium -femoral, femoral-femoral, saphenous-saphenous	— Blood drained from vein and returned to artery. Vein: internal jugular, femoral artery: femoral, axillary, subclavian, aorta
Circuit	Connected in series with heart and lung	Connected in parallel to heart and lung
Cardiac Support	yes	No
Cardiac effects	Preload: decreased. Afterload: increased	May reduce right ventricular afterload. No other hemodynamic effects
Arterial PaO2	60–150 mmHg	45–80 mmHg
Indications	Cardiogenic shock	Respiratory failure with preserved cardiac function

acceptable and more commonly seen with single site double lumen cannula where the entry and exit point are close to each other. Factors that can increase the recirculation percentage are position of the cannula (distal to the right atrium), higher pump flow, and low cardiac output.

VA-ECMO

In VA- ECMO, deoxygenated blood is drained into the circuit for oxygenation and ventilation,and returns into the systemic circulation on the arterial side. Thus, VA- ECMO bypasses the heart as well as the lungs, providing both hemodynamic and respiratory support while allowing the native lung and heart to rest and heal. The VA- ECMO mode is similar to the conventional cardiopulmonary bypass used for cardiac surgeries but adopted for a longer period of support. Cannulation can be central or peripheral. In peripheral cannulation, blood is drained from the proximal femoral or jugular vein and returned via the carotid or femoral or axillary artery. The cannulas used are smaller than the central cannulation and can be done emergently at bedside. Central cannulation usually requires sternotomy or thoracotomy and blood is drained from near the right atrium and returned to the proximal ascending aorta. It is a preferred option when used immediately after cardiopulmonary bypass as the same cannulas can be connected to the VA-ECMO circuit.

The cannula position, diameter and length, along with the patient's venous filling, vascular resistance, and pump speed play an important role in the overall blood flow and the hemodynamics. A proportion of the blood flow (~15-20%) can continue to go through the lungs during a VA-ECMO. Therefore, in a patient with poor lung function, the proportion of blood going through the lungs, which are not adequately oxygenated, mix with well-oxygenated blood provided by the ECMO circuit in the aorta. Hence, in the case of peripheral VA ECMO, the coronary arteries, cerebral blood vessels, and proximal branches of the aorta may receive blood with lower oxygen content. Thus, the decision on the location of the cannulas assumes an important role in VA-ECMO [9] in patients with poor lung function.

Indications in Respiratory Diseases ARDS

Extracorporeal life support (ECLS), particularly VV-ECMO, has been used as a rescue therapy in patients with severe ARDS. Though some studies have shown improvement in mortality among ARDS patients over the years, it is still unacceptably high in severe ARDS at 40-52% [10,11]. ECMO started to gain popularity as a rescue therapy in this population since the 2009 H1Ni influenza pandemic. The exact indications for ECMO have varied across institutions. Broadly, it is indicated for refractory hypoxemia on conventional ventilation therapy, severe acidosis, and hypercapnia. The Murray score is a scoring system that includes the chest roentgenogram , PaO_2/FiO_2 ratio, positive end-expiratory pressure (PEEP), and compliance to stratify these patients [12]. According to ELSO (extracorporeal life support organization) guidelines for adult with ARDS [13], ECMO is indicated when despite the optimal care for 6 hours or more, the predicted mortality risk is >80% which is associated with a PaO_2/FiO_2 <150 on FiO_2>90% and/ or a Murray score of 3-4. ECMO should be considered when the mortality risk is >50% which is associated with a PaO_2/FiO_2 <150 on Fio_2>90% and/or a Murray score of 2-3. As of July 2012 [14], the overall survival in adult patients on ECMO for respiratory failure in the past five years ranged from 53% to 61% which is similar to other recent studies [15].

While considering ECMO in patients, one of the most important considerations is the reversibility of the pulmonary disease. Other pre-ECMO characteristics of the patients like advanced age, high ICU severity score, multiorgan dysfunction, immunocompromised status, and poor neurological status negatively impact ECMO outcome [15,16]. Various studies have shown that the earlier the patient placed on ECMO, the better the outcome [17, 18, 19, 20, 21]. Ventilator associated lung injury (VILI) is a significant cause of morbidity and mortality in ventilated patient [22, 23], and reduction in the duration of mechanical ventilation prior to ECMO minimize ventilator associated lung injury and that possibly explains the survival benefit. The ventilator setting while the patient is on ECMO (Table 2) is minimal and lung protective, helps the lung to rest, and reduces VILI.

Table 2. **Ventilator settings while on ECMO**

Peak inspiratory pressure	20–25 cm H2O
Positive end-expiratory pressure	10–15 cm H2O
FIO2	<0.5
Respiratory rate	8–10 breaths/min
Tidal volume	3–4ml/kg

Low volume ventilation prevents VILI in ventilated patients. The problem while on low volume ventilation will be the raising of PCO_2 and acidosis. With the help of extracorporeal CO_2 removal (ECCO2R) technique,

this problem can be overcome. Combining $ECCO_2$ R with low tidal volume ventilation could prove to be the best strategy for management of severe ARDS patients.

Current Evidence

The results of the smaller studies and the first US ECMO multicenter randomized controlled trial conducted by the National Heart and Lung institute in 1974 were discouraging and did not show measurable mortality benefit [24, 25]. In this study, the survival in both conventional and ECMO groups was very poor, only around 10%. These studies were conducted when ECMO technology was primitive. We did not have much understanding in the management of ARDS and was receiving high tidal volume ventilation. However subsequent studies in neonates and children showed a mortality benefit, and it was widely accepted and used in a pediatric population[26, 27].

Some centers continued to work on ECMO in adult populations, and over a period of time, various observational studies demonstrated safe and successful application of ECMO in critically ill adults [28, 29]. The survival rate recorded in the ELSO registery [30] was 41% in 1995, and overall 197 patients had received ECMO for ARDS at that time. This was comparable to European studies published in that time period [31] where around 850 patients received ECMO between 1992-1999. The better outcome with recent studies is attributed to the advanced technology in ECMO as well as the use of low tidal volume lung protective strategies. Morris et al [32] conducted a randomized clinical trial in 1994, which also did not show a mortality benefit as compared with standard therapy. In spite of all the controversies, ECMO gained popularity as a rescue therapy for severe ARDS adult patients during the 2009 H1N1 influenza pandemic [33, 34, 35].

The landmark trial was the CESAR trial [Conventional ventilator support vs Extracorporeal membrane oxygenation for Severe Adult Respiratory failure] [36] concluded in 2006 and published in 2009. It is the major randomized control trial and the first in the literature to show a mortality benefit in patients who were transferred to an ECMO. A total of 180 patients were randomized 1:1 to two groups. A control group continued to receive the conventional ventilation therapy at tertiary care centers, while the intervention group was referred to an ECMO center for consideration of ECMO. Among the 90 patients that were transferred to a center with ECMO capabilities, only 68(75%) patients received ECMO and of which, 63% (57/90) patients survived to six months without disability, compared to 47% (41/87) of those that received conventional therapy (RR 0.69%, 95%CI 0.5-0.97, p=0.03).

There are two major criticisms to the above study. The intervention in the CESAR trial was. referral to a center with ECMO capabilities rather than treatment with ECMO, and actually 25% of the intervention group did not actually receive ECMO. The other major criticism is that the study did not dwell on the management of the patients in the conventional ventilation arm, and it is unclear as to how many patients received low tidal volume lung protective ventilation.

The Australia and New Zealand ECMO Influenza Investigators [33] reported their experience in treating the 2009 outbreak of H1N1 Influenza infection that led to a number of young otherwise healthy patients developing severe ARDS. Among 201 intensive care unit patients in the study, 68 (30%) received ECMO. The mortality in this group was 21% (14 patients), compared with 9% on the non-ECMO group. This accompanies other papers that failed to show a mortality benefit [36, 37]. Meanwhile, other studies showed a mortality benefit [39, 40]. This conflicting evidence necessitated a large multicenter randomized controlled trial that can prove or disprove the benefit of ECMO.

The French group REVA (Research Network on Respiratory Failure and Artificial Ventilation) is conducting the EOLIA study (ECMO to rescue Lung Injury in ARDS), an international multicenter randomized controlled trial in patients with severe ARDS, which is an attempt to provide better evidence. Patients are promptly randomized into ECMO and conventional therapy groups in which the limitations of the CESAR trial are addressed. The results of this study are eagerly awaited.

Chronic Obstructive Pulmonary Disease

In chronic obstructive pulmonary disease (COPD), invasive mechanical ventilation is associated with many complications including ventilator associated pneumonia, dynamic hyperinflation of lungs, ventilator dependence, and impaired delivery of aerosolized medications[41, 42]. A modality of ECLS includes extracorporeal carbon- dioxide removal (ECCO2 R) that helps remove carbon dioxide (CO_2) from the circulation. ECCO2R is an intermediate level of ECLS with little technical difference than the complete ECLS provided by ECMO. The blood flow is lower (0.3-0.5litres/min) and able to remove ~25% of CO_2. It has been shown

to reduce the need of invasive mechanical ventilation (IMV) and has also been used to assist removal of CO_2 in patients already on mechanical ventilation, in an effort to reducethe number of days on the ventilator and intensive care unit stay.

A pump-less ECCO2 R A-V circuit has been used to prevent mechanical ventilation in patients in severe exacerbations of COPD [43, 44]. This modality has also been used as a supportive therapy for patients who are already on mechanical ventilation to facilitate early extubation, early mobilization and physiotherapy, even while on ECCO2 R [45, 46, 47]. A feasibility pilot study was done to assess the possibility of early extubation and early ambulation in patients receiving mechanical ventilation using single site ECCO2R, with excellent results. Further studies are required to define the criteria and the patient population that would most benefit from this modality.

ECMO as a Bridge to Lung Transplant

Lung transplant waiting lists are increasing, and there is severe paucity of suitable organ donors. Patients with end- stage lung disease awaiting transplant who are failing medical management need a bridge until a donor becomes available. ECMO helps transitioning of care before, during and after the transplant procedure. The initial concept of bridging originated with left ventricular assist devices (LVADs) for cardiac transplant [48, 49]. Initial studies of patients on ECMO had poor perioperative outcomes [50]. Recently, ECMO has been used safely in patients during transplant and aid their recovery [51-52]. ECMO and ECCO2 R modalities have been used to reduce the need for mechanical ventilation and help participate in rehabilitation and physiotherapy, which has further improved outcomes. It also helped to avoid ventilator-associated complications [53].

Experiences from large academic centers and from international centers have come in throughout the last decade, with many showing improved survival and favorable outcomes. The university of Kentucky and the university of California successfully bridged 31 patients as of 2013 and achieved a 80% 3-year survival [54]. The university of Pittsburgh has used ECMO as a bridge for 31 patients with 25 surviving to transplant. This group demonstrated a 74% survival in the ECMO group [55]. A French group reported their experience with lung transplant with ECMO in 36 patients with 30 making it to transplant. The 2-year survival was reported as 60.5% but outcomes in patients with cystic fibrosis was significantly better than in those with idiopathic pulmonary fibrosis (IPF). This observation suggests that ECMO outcomes may vary depending on the underlying etiology of the lung disease [56].

Extracorporeal Cardiopulmonary Resuscitation

Extracorporeal cardiopulmonary resuscitation (E-CPR) is the term used for institution of ECLS during cardiopulmonary resuscitation to help return of spontaneous circulation (ROSC). A growing body of evidence suggests the utility of ECLS in cardiopulmonary resuscitation in improving outcomes and survival in patients with intra-hospital cardiac arrests (IHCA) and out of hospital cardiac arrests (OHCA)[57, 58, 59, 60]. In prospective observational trials of IHCAs, survival to discharge varied from 20% to 32%, with p values of <0.0001 and 0.002 respectively [57, 58] with a good neurological outcome. Similarly, out of hospital arrests also showed comparable outcomes, with survival of 29.2% at 3 months and a p value of 0.018 [57]. The recently published prospective pilot study, The CHEER trial [61] was carried out for refractory IHCA and OHCA in Australia. These patients had a ROSC of >30 minutes with an initial rhythm of ventricular fibrillation. The reported survival rates were 54% with 13 out of 24 patients surviving to hospital discharge. Further studies are ongoing, so that we can further delineate the patient populations with the most expected survival benefit.

Pulmonary Hypertension and Pulmonary Embolism

ECLS has been used as an emerging therapy in patients with severely decompensated right ventricular (RV) failure and pulmonary hypertension of various etiology. ECMO may be implemented briefly to support the patient while medical management is being optimized during a crisis or as a bridge for lung transplant [62]. Commonly, VA- ECMO is applied, which will decompress the right ventricle, leading to reduction in right ventricular pressures and also preferentially shunts the blood into the ECMO circuit leading to better oxygenation and ventilation [63]. It can provide a bridge to successful lung transplantation in World Health Organization group I pulmonary artery hypertension patients with end-stage cardiopulmonary failure. A retrospective review of use of ECMO for massive pulmonary embolisms in 21 patients demonstrated improvement in survival to 62% when used along with conventional medical management [64].

This improved survival has been supported by other published cases [65].

Future Directions

The most important implication of ECLS is early mobilization, early rehabilitation and early physiotherapy, which has time and again showed to positively impact clinical outcomes [66, 67]. This, along with reduced ventilator requirements and hence less associated complications like VILI will prove to be more beneficial to select groups of patients [68, 69]. As of now, ECLS is being used only in select centers as a rescue therapy for refractory respiratory failure, cardiogenic shock and as a bridge to lung and heart transplant. Advancements in technology in manufacturing of circuitry will lead to compact consoles and ambulatory ECMO machines as a destination therapy for end stage lung disease. The expanding utility of ECLS is rapidly encompassing all forms of respiratory failure from various causes and severe right ventricular failure.

Weaning of ECMO

Weaning from ECMO is a crucial step, and there are no standard protocols as of yet. It is basically provider dependent and usually based on some rough guidelines from scientific societies. Weaning from VA ECMO and VV ECMO are different. However the most basic requisite before weaning is the recovery of the lung and or cardiac function significantly so that the lung and or cardiac rest is no longer needed.

In VV ECMO, weaning is a process where contribution of ECMO to gas exchange (oxygenation and CO_2 removal) is progressively decreased while the native lung takes over its function. The actual circuit blood flow need not be altered to assess the pulmonary function. The clinical parameters that can indicate recovery of pulmonary function [9] are (a) progressive increase in SaO_2 above SvO_2, (b) improvement in $SaO2_{for}$ a given circuit gas flow or a reduced gas flow, (c) improvement in respiratory mechanics - lung compliance, airway resistance, (d) radiological improvement. ELSO guidelines indicates that when the native lung can support 50-80% total gas exchange at a moderate ventilator setting (FiO_2 <0.6-0.5, low PEEP) ECMO discontinuation can be considered. Weaning from VV ECMO (Table 3) is performed by progressively decreasing the gas flow to the oxygenator. At zero flow, if the patient able to maintain stable hemodynamic and ventilator parameters for 4-24hours (varies from center to center) then the patient can be effectively off of ECMO. Extracorporeal support can be then discontinued and decannulated. The goal is to resume mechanical ventilation with ventilator settings that are less injurious and can maintain good oxygenation and ventilation, which would have been impossible prior to initiation of ECMO. Weaning is generally possible in ARDS after 7-10 days on ECMO.

Table 3. **Weaning VV-ECMO in respiratory failure**

• Sweep gas flow set at 0 L/min • FiO_2 set at 0.21 on the membrane • Pump flow not modified	The device may be withdrawn if — PaO2 >60 mmHg, SaO2 >90 % — FiO_2 on the ventilator <60 % — Inspiratory plateau pressure <30 cm H2O For at least 1–2 hours and up to 12 hours

If the patient is on VA-ECMO and the indication of ECMO is for cardiac causes, the myocardial recovery is required before weaning can be initiated. The parameters need to be monitored in these patients are (a) return of pulsatile arterial pressure waveform for 24hrs, hemodynamic stability with baseline mean arterial pressure greater than 60 mmHg in the absence or with low doses of catecholamine (b) decreasing central venous and/or pulmonary pressures (c) improvement of pulmonary function, $PaO2/FiO_2$ <100mmHg. Weaning in VA ECMO is carried out by reducing blood flow through the circuit hourly. Once the blood flow is as low as 1-2 liters/minute and the patient has been hemodynamically stable for few hours, surgical decannulation may be carried out. Doppler echocardiography parameters help in assessing cardiac function while weaning.

Successful weaning from ECMO depends on the underlying cause, it's reversibility, associated comorbidities, and severity of organ dysfunction at the time of ECMO initiation.

Complications on ECMO

Application of ECMO is associated with number of complications. A specialized center with extensively trained personnel and well-experienced staff is required to implement it safely to demonstrate the survival benefit. Improvement in technology and the circuit has decreased complications rate over the past decade. The Extracorporeal Life Support Organization (ELSO) database[14] gives us the rates of complications of patients on ECMO and guidelines to follow for their management. Complications can be broadly classified as physiological and mechanical (Table 4).

The most common complications among them are clot formation and bleeding. As blood passes through

Table 4. **Complications of ECMO**

Physiological complications	Mechanical, related to circuit
Bleeding — cannula site — Intracranial, GI, Pulmonary Thromboembolic Hemolysis Neurologic — seizures, stroke, encephalopathy	Failure of oxygenator Pump failure Cannula problems

the circuit, activation of clotting factors and emboli is a major concern. Anticoagulation is usually done by heparin drip, maintaining activated thromboplastin time of 1.5 times normal values. The reported incidence is 12-17%. Localized bleeding from the cannula insertion site (16%) or from the surgical site (17%) is common and can be managed with simple compression. Major bleedings like intracranial bleeding is reported in 3.9%, pulmonary and gastrointestinal bleeding reported in 8% and 5%, respectively. The hematologic consequences of an ECMO circuit include hemolysis, acquired von Willebrand factor deficiency, and thrombocytopenia contributes to the bleeding and thrombotic risks. After hematological adverse effects, infection remains the significant problem with a reported rate is 21.3%. The other potential complications are encephalopathy, renal dysfunction, and liver injury.

The complications of VA-ECMO are similar to VV-ECMO, with added possible complications (a) pulmonary hemorrhage (b) cardiac thrombosis and (c) limb ischemia from peripheral arterial cannulation. When the left ventricular contractility is poor, the left ventricle continues to dilate from persistent preload and the left ventricular end-diastolic pressure increases. This in turn increases the pulmonary pressure causing pulmonary hemorrhage. With VA- ECMO the pulsatility of the blood flow is lost, and blood stagnates in the aortic root ,increasing the risk of cardiac thrombosis and systemic emboli.

Ethical Considerations

The patients' families must be extensively educated about the process of ECMO and counseled about the possibility of unfavorable outcomes, in spite of the extraordinary measures being taken to maintain life Even after a successful recovery from ECMO, the neurological outcome may still be poor. End of life discussions must be held, either with the patient, or with health care surrogates. The goal of care should be well established as families may wish to continue therapy even if the treating team feels that the patient's condition has progressed to an irreversible state. Daily updates and clear discussion about the prognosis with patients and their families help in avoiding such situations.

Conclusions

Every day, significant advances continue to be made in the field of ECLS. The modality promises to supplement the management options available for severe cardiac and respiratory disease. More widespread data from multiple centers are needed to add to current knowledge and help us understand its role in management of different patient populations and its potential indications.

Conflict of interest: None declared.

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