Symposium

Extracorporeal membrane oxygenation: A review

Praveen Khilnani*

*Director PICU fellowship program BLK Superspeciality hospital, Delhi and HOD Pediatric intensive care, Mediclinic city hospital, Dubai, UAE

Received: 01-Mar-17/Accepted: 03-Apr-17/Published online: 05-May-17

ABSTRACT:
Extracorporeal membrane oxygenation (ECMO) is used to support heart and lungs for extended periods of time till the underlying disease process is treated by use of a semi permeable membrane oxygenator. In 70s ECMO as a treatment modality in adult respiratory failure did not gain universal popularity due to no difference in outcomes when compared to conventional ventilator management. In the same period, however, neonates, especially those with persistent pulmonary hypertension of the newborn (PPHN) showed marked improvement in outcomes. Since 2009 there has been a resurgence of ECMO secondary to outbreak of H1N1 Influenza leading to severe hypoxic respiratory failure. Currently ECMO is considered as a valid alternative if there is a failure of conventional therapies. This article reviews the use of ECMO with specific indications and management strategies with respect to Pediatric ECMO mainly. Actual equipment of ECMO has also evolved over time to be smaller and with better precision. Development of biocompatible oxygenators and coated circuits to reduce the complications of consumptive coagulopathy and thrombocytopenia. The shift from roller pump ECMO machines, which are mainly gravity dependent for achieving flow to magnetically driven centrifugal ECMO pumps, has made noticeable change to the practice. In the last part of review Indian scenario and setting up of an ECMO program is also discussed briefly.

Key words: ECMO, extracorporeal membrane oxygenation, Venovenous ECMO, respiratory ECMO, Venoarterial ECMO, Cardiac ECMO

Extracorporeal membrane oxygenation (ECMO) is a modification of conventional cardiopulmonary bypass used to support heart and lungs for extended periods of time till the underlying disease process is treated. Use of a semi permeable membrane oxygenator to prevent direct contact of blood and gas, to prolong extracorporeal support is well established. Clinical reports of long-term membrane extracorporeal support of patients with respiratory failure were described in the early 1970s. ECMO as a treatment modality in adult respiratory failure did not gain universal popularity due to no difference in outcomes when compared to conventional ventilator management. In the same period, however, neonates [especially those with persistent pulmonary hypertension of the newborn (PPHN)] had improvement in outcomes secondary to ECMO, although premature babies at less than 35 weeks gestation had an unacceptably high incidence of intracranial hemorrhage. Since then, ECMO as a rescue treatment modality for infants over 35 weeks gestation and children has grown and become increasingly popular in intensive care units (ICUs). Since 2009 there was outbreak of H1N1 Influenza leading to severe hypoxic respiratory failure where ECMO technology showed promising result in improving mortality, leading to resurgence of use of ECMO both in adults and pediatric age groups 2-3. Currently ECMO is considered as a valid alternative if there is a failure of conventional therapies.

Robert Bartlett in Michigan (USA) was the first physician to use neonatal ECMO successfully in 1972 in a case of meconium aspiration syndrome. The baby girl was named as Esperanza (meaning, hope in Spanish). The ECMO has been revolutionized since then. From venoarterial ECMO, which has been the norm for all reversible pathologies, physicians are shifting towards venovenous ECMO for respiratory pathology not needing cardiac support, which is more physiological in application for non-cardiac conditions. The size of the circuits has been miniaturized since then, besides further development of biocompatible oxygenators and coated circuits to reduce the complications of consumptive coagulopathy and thrombocytopenia. The shift from roller pump ECMO machines, which are mainly gravity dependent for achieving flow to...
magnetically driven centrifugal ECMO pumps, has made noticeable change to the practice. The advances ensuing further reduction in size of the components resulted in compactness of the entire system, making it much more friendly to use for transport as mobile ECMO. All these innovations have benefited our patients remarkably, leading to improvement in their outcomes.

Indications of ECMO:
The ECMO can be used for rescuing patients following respiratory or cardiac conditions. Sometimes, it could be a combination of both. Cardiac indications have been limited to children with intractable cardiac failure after cardiothoracic surgery, but the use has been increased in patients with severe viral myocarditis, toxic myocardial depression and intractable arrhythmias. Patient outcomes depend mainly on the etiology of the cardiac failure. Overall, there has been an increase in the number of these indications resulting in better outcomes, which is probably due to increased experience. Most recently, ECMO has been used as a tool for resuscitation on patients with cardiopulmonary arrest (4) and some centers have used ECMO for support of donor abdominal organs. The prediction of mortality in pediatric patients is more difficult due to the coexistence of multiple organ failure. Matching for diagnosis and severity of illness, ECMO-treated patients had a 74% survival vs 51% survival in non-ECMO-treated patients. This study shows that when used appropriately, survival in some patients is enhanced by ECMO. Determining that a patient is unresponsive to maximal medical therapy and considering the use of ECMO remains difficult and controversial. Most criteria have evolved from the neonatal ECMO experience.

Respiratory ECMO:
Eligibility Criteria for Respiratory ECMO:
Reversible respiratory failure is an absolute basic requirement to consider ECMO in any patient. Sometimes, the ‘irreversibility factor’ might be unclear at the time of initiation of ECMO, but might become evident at a later stage. It emphasizes the fact that ECMO is only a support mechanism to help the patient, while allowing the underlying disease process to heal. The patient should have been treated with maximal conventional support for the optimal time period before considering ECMO. When the conventional therapy is not working, patient should be offered ECMO. The dialogue between treating physician and ECMO physician is of paramount importance to select the right patient and treat them with ECMO at the right time, avoiding undue delay. Cost remains a major issue in our country, however considering the significant mortality benefit, it is a therapy worthy of serious consideration, if the primary problem is a reversible one. Patient should not have any contraindication for anticoagulants like heparin. There should not be any intracerebral bleed or intraventricular bleed greater than grade 2 (in premature term newborns or infants).

Respiratory ECMO Indication:
Clinical indications of ECMO for respiratory conditions in pediatrics are as follows:
- Severe acute respiratory distress syndrome (ARDS), refractory to maximal conventional treatment stands out as the major factor for which we consider respiratory ECMO. The etiology of ARDS might differ. It could be secondary to viral pneumonias, bacterial pneumonias, malaria, tuberculosis or viruses. In recent days, the efficacy of ECMO in supporting patients with H1N1 has been very well-established.
- Meconium aspiration syndrome.
- Severe bronchiolitis.
- Inhalation pneumonia (postburns).
- Post-traumatic lung contusions.
- Acute chest syndrome (sickle chest).
- Status asthmaticus.
- Persistent air leaks.
- Reactive pulmonary hypertension in neonatal period (reversible).
- Congenital diaphragmatic hernia.
- Near drowning, etc.

Respiratory ECMO Selection Criteria:
Presence of any two criteria from the following, observed over a period of 4–6 hours after using maximum medical resuscitation measures may help us in selecting the patients. These criteria provide us with
guidance. The overall assessment of an experienced physician in evaluating the progression of the disease is more important in selecting the right patient who will be benefited by ECMO.

The respiratory ECMO selection criteria are as follows:

- Partial pressure of O2 in arterial blood (PaO2)/fraction of inspired oxygen (FiO2) ratio of < 75%
- Oxygen index of > 40 for 4–6 hours
- Murray’s score 2 of > 3.0
- Alveolar-arterial (A-a) gradient > 600 mm Hg
- Lung compliance < 0.5 cc/H2O/kg
- Ventilation index > 40 for 4 hours.

Exclusion Criteria

- Irreversible disease—malignancy with poor outcome
- Patient on ventilator for > 10 days (lung fibrosis is likely to set in)
- Significant intracranial bleed
- Patient in gross multiple organ failure (relative)
- Severe central nervous system (CNS) injury including encephalitis, persistent vegetative state where the neurological outcome is expected to be dismal.

Cardiac ECMO

Cardiac ECMO Indications

Reversible cardiac failure includes:

- Acute reversible refractory cardiac failure situations
- Preoperative stabilization
- Failure to weaning from cardiopulmonary bypass
- Low cardiac output syndrome (postoperatively)
- Myocarditis (postviral, poisonings like scorpion sting, etc.)
- Intractable arrhythmias
- Postcardiac arrest
- Reversible pulmonary hypertension.

It is indicated in irreversible cardiac diseases only as a bridge to ventricular assist devices like Berlin heart or those awaiting urgent heart transplantation. In countries such as India and Africa, since pediatric heart transplant facilities are underdeveloped, only reversible cardiac conditions such as postcardiac surgery operative low cardiac output or myocarditis would be applicable indications for cardiac ECMO.

ECMO Selection Criteria for Cardiac Support

Strict criteria for the usage of ECMO in pediatric cardiac failure are not available. None of the published severity of illness markers or clinical parameters has been proven to universally predict outcome, but may remain of assistance when trying to identify patients who might be benefited by extracorporeal life support (ECLS).

Presence of any two criteria from the following, observed over a period of 4–6 hours after maximum conventional management might be helpful in selecting the patients who will be benefited by ECMO.

Following are the criterias for the selection of ECMO for cardiac support:

- Refractory arrhythmias
- Cardiogenic shock with high-inotropic requirements (more than 20 points as per inotropic score)
- Lactate level > 50 mg/dL or 5 mmol/L or rising titer or central venous oxygen saturation (ScvO2) < 60%
- pH less than 7.15 with oliguria (< 1 mL/kg/h) in spite of intra-aortic balloon pulsation (IABP) and inotropic supports in selective group of patients
- Cardiac index < 2 L/min.

There is a miscellaneous group of disorders like septic shock, poisoning due to beta blockers, calcium channel blockers overdose, etc. which are refractory to maximal conventional management that might be benefited by venoarterial ECMO, allowing time for recovery.

There is renewed interest in the understanding and practice of ECMO in India. It is feasible to do it in selective intensive care units, geared up to accept the challenges, work in teams and achieve the benefits.

Figure 1 shows the currently published international ELSO registry data of pediatric and adult, which is showing survival ranging from 55%–64% in adults and 65%–85% in pediatric age group depending upon cardiac or respiratory indication.
ECMO cardiopulmonary resuscitation (ECPR) is being carried out at many western hospitals with pediatric survivals as good as 54%–63%. Few centers in India have begun participation in ELSO registry and an Asian chapter also has recently been formed (refer Fig. 1).

**Technique of ECMO:**

**The two basic types of ECMO are venoarterial (VA) and Venovenous (VV).**

This terminology describes the direction of blood flow. The outflow is always venous, but the inflow can be arterial or venous. Outflow of blood in VA and VV ECMO is from the right atrium through a catheter placed through the right internal jugular vein. In older patients, other venous sites have been used. In VA mode, after oxygenation in the ECMO circuit, the blood is returned to the patient through an arterial cannula, which is placed in the ascending aorta through the right common carotid artery (Fig. 2). A cannula can also be placed directly into the right atrium and the aorta through a sternotomy. Patients with profound left ventricular failure need a left atrial or ventricular catheter to obtain decompression of the left heart. The artery that was cannulated is permanently ligated. The effect of this is unknown. Some centers have begun repairing the artery at decannulation. Repairs had an early patency rate of 90% in some centers. Patients with normal cardiac function, as well as those with severe pulmonary disease, may be candidates for VV ECMO support.

Cannulation is done at the bedside under deep sedation and analgesia. A double lumen venous cannula has been used in neonates; and in adults, the blood is returned to the distal iliac vein of the inferior vena cava. The blood first enters a small bladder that is attached to a servo-regulated box connected to a roller pump. Inadequate blood return triggers an alarm on the bladder box, which in turn, shuts the pump off. When the bladder refills, the pump restarts. This process prevents excessive negative pressure, which otherwise might result from a kinked cannula or hypovolemia and more importantly, prohibits the formation of air bubbles. After exiting the bladder, the blood is actively pumped by a roller pump into a membrane oxygenator.

The oxygenator consists of a hollow silicon envelope placed inside a silicone sleeve. The blood flows on the outside of the coiled envelope and the gas flows in a countercurrent direction inside the membrane. The size of the membrane is chosen according to patient size. There is an effective gas exchange here. Next, the blood flows into a heat exchanger and then, it is infused back into the patient.

The ECMO circuit is designed with a bridge that allows the child and the circuit to be isolated from one another. The blood is heparinized, and the heparin effect is measured by activated clotting time (ACT), which is maintained at 180–220 seconds. ACT can be measured at the bedside.

![Figure 1: Extracorporeal life support organization 2017 data (ECPR, extracorporeal membrane oxygenation cardiopulmonary resuscitation).](image-url)
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Figure 3: ECMO equipment in PICU
Figure 4: Cannula – double lumen

Figure 5: 13,15,18fr Canulas

Figure 6: Quadrox Oxygenator

Figure 7: Centrifugal Pump

Figure 8: Portable Heart Lung support system
Management of ECMO:
Patient management is supportive and all principles of pediatric critical care apply:

- Initiation
- Fluids/RRT/nutrition: Sedation/analgesia:
- Ventilator management
- CO2 removal by sweep gas flow
- Antibiotics
- Anticoagulation and Monitoring for clots
- Weaning ECMO flows
- Decannulation
- Post-ECMO care: Ventilation…CMV or HFOV

Initiation of ECMO:
Under sedation and neuromuscular blockade an initial bolus of heparin (100–200 unit) is given just prior to the cannulation after which a heparin infusion is started and continued throughout the duration of the ECMO. The flow is initially started low by 50 mL/kg/min and gradually increased by 50 mL increments. Infants need 100–200 mL/kg/min for adequate perfusion and oxygenation, although there are patients who may need more. Pediatric patients usually need 90 mL/kg/min to achieve the same goals.

In VA ECMO, as the flow is increased, the left ventricular output decreases and the arterial waveform becomes less pulsatile. Stored blood is used to prime the circuit, which may be acidic and calcium depleted. Using tromethamine (THAM) or bicarbonate in the priming fluid can correct acidosis. It is also recommended to measure the electrolyte concentration of the stored blood. Patients will need intermittent blood products transfused. Fresh frozen plasma may be needed intermittently to replenish clotting factors.

The ECMO circuit also sequesters platelets, and counts of 80,000–100,000 are maintained routinely.

Adequacy of nutrition is maintained by initiation of hyperalimentation and early enteral feeds are not a contraindication. Diuretics may be needed to prevent fluid retention.

Renal replacement therapy with hemofiltration or hemodiafiltration can be effectively instituted in ECMO circuit.

Ventilator management:
While on a ventilator, patients are placed on relatively non-traumatic settings to promote lung healing. A peak inspiratory pressure (PIP) of 18–20 mm H2O, with a positive end-expiratory pressure (PEEP) of 4–5 mm H2O, is generally used. The ventilator rates are set at 6–12 breaths per minute and the FiO2 is 25%–30%. Sometimes, older children are managed with a PEEP of 10–12 mm H2O to prevent loss of functional residual capacity. Tolerate pCO2 55–65, SpO2 > 88%.

Time of “rest” depends on process (generally 3–5 days minimum for ARDS)

Suctioning may be performed as needed with a closed suction system. One should avoid manual bagging to avoid alveolar derecruitment.

Resolution of air leak occurs in 48–72 hours. Patients with barotrauma and air leak may benefit from high-frequency ventilation, in addition to ECMO. Typically, neonates benefit from low mean airway pressure and lung rest, and pediatric patients benefit from maintenance of functional residual capacity with higher PEEP. For CO2 removal sweep gas flow in the ECMO circuit can be regulated.

Antibiotics: As a part of treatment for sepsis, appropriate antibiotics need to be continued based on cultures and clinical status, however routine use of prophylactic antibiotics is not recommended.

Anticoagulation:
Since blood is heparinized, the heparin effect is measured by activated clotting time (ACT), which is maintained at 180–220 seconds. TEG (thromboelastogram) is now available at many centres for coagulation monitoring.

Weaning ECMO flows and Decannulation:
When the underlying process improves, the patient is weaned to low ECMO flows (50–100 mL/kg/min) and optimal ventilator settings. A decision to decannulate is made after the patient maintains adequate oxygenation and perfusion in these settings for 2–4 hours. This weaning of flow can be achieved in slow reductions of flow rate by increments of 10–20 mL/kg/min every 1–2 hours, up to a flow rate of 50–100 mL/kg/min. During the process of weaning, blood gases and the mixed venous saturations should be frequently monitored. A more rapid weaning rate can be achieved by decreasing the flow in larger increments over shorter time intervals. Once a flow...
rate of 50–100 mL/kg/min has been achieved, the patient is monitored for a few hours. If deterioration is seen, high flow is re-established for 24 hours before a repeat trial is performed.

**ECMO management summary:**
- After cannulation and establishing ECMO flow
- Change Ventilation to minimal setting: rate of 5-8 and PEEP to prevent atelectasis.
- Monitor vitals
- Monitor ACTs, and
- Daily Na K Ca KFT Chest Xray
- Pre and post ECMO gases.
- patient ABG,SpO2
- Strict IO,
- Urine output,
- Sedation as necessary
- Monitor for Block/Clots in circuit
- CO2 control by sweep gas flow
- Cardiac output and Oxygenation by ECMO flow (in VA ECMO)
- Oxygenation by ECMO flow in VV ECMO
- Wean ECMO flow… Decannulation when condition improves

**Complications of ECMO:**

**Mechanical Complications:**
The most common mechanical problems are oxygenator failure, tubing rupture or leak, cannula kinking, power failure, air in the circuit and accidental decannulation.

**Patient Complications:**
Bleeding from heparinization is a common complication. Intracranial hemorrhage is catastrophic. Daily head ultrasounds are performed on infants with open fontanels. As any other site can be involved just as easily, a high index of suspicion is needed. Since infection is also problematic, frequent surveillance cultures are ordered on all ECMO patients. Prophylactic antibiotics are not used to treat infection. Embolization is another risk, especially with VA ECMO; and can consist of a clot, air or particulate matter. A bubble trap is added to the arterial side of the circuit in an attempt to reduce this risk. Sensorineural hearing loss is a long-term complication with a reported incidence rate as high as 24%. Additionally, there is the possibility of catastrophic technical mishaps like catheter rupture, kinking of canulae, power disruption and accidental decannulation.

**Outcomes:**

**Newborns:**
Infants with meconium aspiration syndrome have had the highest survival rate (71%) compared with other diagnoses analyzed (26.3%; p < 0.001). The most common diagnosis associated with prolonged ECMO support in neonates is congenital diaphragmatic hernia (CDH; 69%). Nonsurvivors were more likely to experience complications on ECMO, and multivariate analysis showed that the need for inotropes while on ECMO support was independently associated with mortality. Neonates requiring prolonged ECMO support have a 24% survival to discharge. Many of these cases involve CDH. Complications are common with prolonged ECMO, but only receipt of inotropes was shown to be independently associated with mortality.

**Pediatric:**
In one study from Germany, by 31 December 2014, over 900 patients had been treated, the vast majority for respiratory failure, and over 650 patients had been transported during ECMO. The median ECMO duration was 5.3, 5.7 and 7.1 days for neonatal, pediatric and adult patients, respectively. The survival to hospital discharge rate for respiratory ECMO was 81%, 70% and 63% in the different age groups, respectively, which is significantly higher than the overall international experience as reported to the Extracorporeal Life Support Organization (ELSO) Registry (74%, 57% and 57%, respectively).

**H1N1 adult outcomes:**
180 adult patients, randomized controlled trial, intention to treat ECMO showed improved survival at 6 months (63% vs. 47%)(Peek GJ et al CESAR trial collaboration Lancet ,2009). 80 ECMO referrals, H1N1, propensity-matched controls, showed improved survival (76% vs. 53%)ECMO when compared to conventional ventilator management2

**ELSO registry analysis jan2017:**
Overall survival to discharge as per ECLS registry is 73%, 40% and 40% in newborns for respiratory, cardiac and E-CPR indications respectively. Survival to discharge in Pediatric age group was 57%, 50% and 41% for Pulmonary, cardiac and E-CPR indications.
respectively.

**Setting up an ECMO program:**
Evidence shows better outcomes in high-volume centers with rapid turnover of patients. Skills have to be maintained in low-volume centers by attending review courses, simulation, and water labs. As the number of patients requiring ECMO in any bigger city is going to be a fraction of ventilated cases, at present, we would like to recommend it as standard of care in high-volume cardiothoracic centers. Though ECMO is a multidisciplinary speciality, invariably one tends to need some help from surgeons, more so from cardiac surgeons. One will need echocardiographic guidance in the form of regular assessment of cardiac function and watching parameters for resolution of pulmonary hypertension. The ELSO has published guidance on establishing ECMO centers. Though they are universally applicable, minor modifications to suit the sociocultural and economic climate in resource-limited countries may be necessary.

**ELSO Guidelines Regarding ECMO Centers**
1. The ECMO centers should be located in tertiary centers with a tertiary level neonatal intensive care unit, pediatric intensive care unit and/or adult intensive care unit.
2. The ECMO centers should be located in geographic areas that can support a minimum of six ECMO patients per center per year. The cost effectiveness of providing fewer than six cases per year combined with the loss or lack of clinical expertise associated with treating fewer than this number of patients per year should be taken into account when developing a new program.
3. The ECMO centers should be actively involved in the ELSO, including participation in the ELSO registry.

**General Structure:**
The ECMO center should be located in a tertiary level intensive care unit (ICU) with the following components:
1. There should be a single physician ECMO program director with responsibility for the overall operation of the center. While there may be several associate directors with specific interests or focus in limited areas of ECMO care, the primary medical director should be responsible for assuring appropriate specialist training and performance, directing quality improvement meetings and projects, assuring proper and valid data submission to ELSO, and should also be responsible for the credentialing of other physicians who care for ECMO patients or who manage the ECMO circuit.
2. There should be an ECMO coordinator with responsibility for the supervision and training of the technical staff, maintenance of equipment, and collection of patient data.
3. The multidisciplinary ECMO team should have quality assurance review procedures in place for annual ECMO evaluation internally.
4. Formal policy and procedures outlining the indications and contraindications for ECMO, clinical management of the ECMO patient, maintenance of equipment, termination of ECMO therapy and follow-up of the ECMO patient should be available for review.
5. Appropriate laboratory space for training and continuing medical education should be available.

**Indian scenario and future of ECMO:**
In India many centers have started acquiring ECMO technology, however cost remains a major issue. Survival benefit with appropriate early institution in selected patients is the real motivating factor. With portability of the equipment and availability of personnel and proper training of ECMO specialist (intensivist or anesthesiologist or a surgeon), round the clock critical care nurses and perfusionists, it can be accomplished in tertiary centers with round the clock critical care and ancillary services. Hospital administrative commitment and support is of prime importance for success of any ECMO program.

**Key Messages:**
1. Presently, ECMO is viewed as an invasive procedure with significant risks, and should be used only after careful evaluation of risks/benefits and discussion with the family.
2. It continues to represent an important support option in select critically ill infants and children. In the future, with increased experience, this procedure will become an even safer, more effective alternative to many less efficacious conventional therapies.

**Conflict of Interest:** None

**Source of Funding:** None

**References:**


