Tutorial

Extracorporeal membrane oxygenation — An anesthesiologist's perspective – Part II: Clinical and technical consideration

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ABSTRACT

Summary: Although the concept of extracorporeal membrane oxygenation (ECMO) has remained unchanged, component technology has evolved considerably over the past three decades. Presently the clinical conditions requiring ECMO support have been updated with input from the outcome data of patient registries. Modern circuit configuration has become less cumbersome, safer, and more efficient. Technological advances now allow prolonged support with fewer complications compared to the past eras and facilitate transition to a single bedside caregiver model, similar to hemofiltration or ventricular-assist devices. The clinical considerations and indicators for placing the patient on ECMO, the various circuit configurations, clinical and technical issues, and management aspects are considered in this article.

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SYNOPSIS OF PART - I

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This article intended to cover the history with evolving concept on ECMO and varoius acronyms for the variants of this extracorporeal life support, aiming for an easy understanding of the working principles along with the physiological aspects taken into consideration. The topic was divided into subheadings covering the principles and types of circuit, physiology of O_2 and CO_2 exchanges, associated hemodynamic changes, physiological variables pertaining to tissue oxygenation, drug disposition, predictors of mortality, morbidity and research with future avenues targeting the physiological principles being enumerated.

INTRODUCTION

The ECMO equipment and their mode of application have changed and evolved over time, but the basic concept of continuous extracorporeal circulation of blood to provide gas exchange and perfusion still remains the same. In the current scenario, treatment using extracorporeal gas exchange is necessitated for a combined cardiorespiratory compromise that is life-threatening and is predominantly either a cardiac or a respiratory failure that is progressive, with a persisting low level of tissue oxygenation that is incompatible with life, even after all possible conventional therapeutic interventions. The clinicians routinely encounter and deal with situations that require selecting patients who might benefit from ECMO support. Additionally, they are required to decide on the technical considerations, the type of ECMO support, the anticipated complications, and the expected outcome. In this article, these clinical and technical aspects pertaining to ECMO are addressed.

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Extracorporeal membrane oxygenation: Clinical considerations and criteria

In the various clinical settings, the primary issues that are dealt with quite often are, the identification and selection of that particular subset of patients, who may reap the maximum benefit from ECMO support, and when the conventional medical therapies are failing, but before any irreversible lung or terminal organ damage can occur. The clinical considerations and criteria for initiating ECMO support in adults vary substantially among the centers [Table 1]. Centers use fast entry criteria or slow entry criteria for objective evidence, which are usually modifications of the classic fast and slow entry criteria of the United States ECMO study. They typically include an oxygenation criterion that is assessed at a certain time point during the acute phase of the disease, at a specific respirator setting, and incorporates the compliance of the lung, extravascular lung water, and at times a pulmonary scoring system [Tables 2 and 3].[1-3]

Table 1: Clinical criteria considered for respiratory support using ECMO[42]

Summary of clinical criteria used by the various institutes across the world (any of the criteria can be used):-
Fast entry criteria (used in centers following an aggressive approach)
A) PaO_2<50 mmHg >2 hours with FiO_2-100%
Maximal medical therapy for 24 – 120 hours
or
B) PaO_2/FiO_2<50 mmHg at PEEP≥10 cm H_2O
or
C) PaO_2/FiO_2<70 mmHg at PEEP>10 cm H_2O for 96 hours
or
Slow entry criteria (used in centers following conservative approach)
A) PaO_2<50 mmHg >12 hours FiO_2 60% PEEP >5 cm H_2O, max medical therapy >48 hours
Qs/Qt>30%
CTstat<30 ml/cm H_2O,
or
B) Maximal medical therapy 24-120 hours. PaO_2/FiO_2<50 mmHg at PEEP>10 cm H_2O; Qs/Qt>30% at FiO_2 - 1.0; EVLV>15 ml/Kg; CTstat<30 ml/cm H_2O or recurrent barotrauma
or
C) 48–96 hours after conventional therapy – three out of four criteria fulfilled
-PaO_2/FiO_2<150 mmHg at PEEP>5 cm H_2O for >2 hours
-$PaCO_2$>60 mmHg at Ve>200 ml/Kg
-PIP>40 cm H_2O,
-CTstat<30 ml/cm H_2O and Qs/Qt>30%
or
No differentiation between fast and slow criteria
A–aPO_2>525 mmHg; CTstat<30 ml/cm H_2O; PIP>35 cm H_2O; extended infiltrations on chest X-ray.

A-aPO_2 - Alveolar-arterial difference of partial pressure of oxygen; CTstat - Total thoracopulmonary compliance; EVLW - Extravascular lung water; PIP - Peak inspiratory pressures; Qs/Qt - Intrapulmonary right to left shunt; Ve - Minute ventilation, PaO_2 - arterial blood O_2 tension, $PaCO_2$ - arterial blood CO_2 tension

Choice for the type of extracorporeal membrane oxygenation placement

The algorithm in Figure 1 simplifies the understanding about the choice of the type of ECMO (veno-venous or arterio-venous) the clinical settings.

Extracorporeal membrane oxygenation indications specific to the subgroup

Extracorporeal membrane oxygenation use specific to neonates and infants

Initially, ECMO was most commonly used in neonatal intensive care units for pulmonary distress [Table 4]. However, with passing time and a better understanding

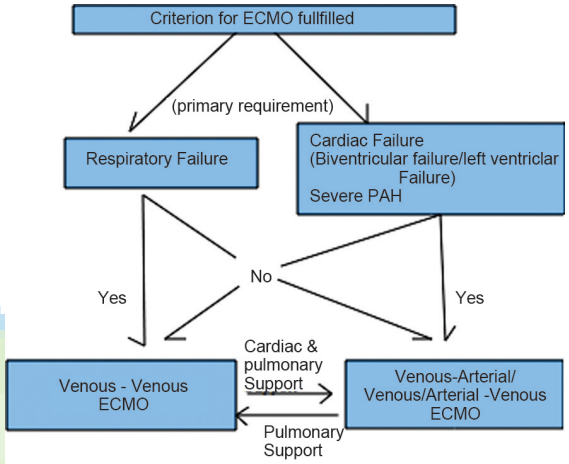


Figure 1: Understanding the choice of ECMO

Table 2: Clinical criteria considered for cardiac support using ECMO

Inadequate tissue perfusion - low-cardiac output syndromes
Mixed venous PA saturations <50%
Cardiac index <2 L/ minute/m^2 impending multiorgan dysfunction
Metabolic acidosis (refractory)
Inotropic support (supramaximal doses)
Myocarditis
Peripartum cardiomyopathy
Decompensated refractory myocardial failure

PA - Pulmonary Artery

Table 3: General exclusion criteria for ECMO

Terminal disease
Irreversible central nervous system injury or malformation
Recent neurosurgical procedure < 10 days
Intracranial hemorrhage - Grade II or more
PaO_2 / FiO_2< 100 for > 10 days (infants)
> 5 days (adults)
Immunodeficiency
Chronic myocardial dysfunction and not a candidate for transplantation
Multi-organ Dysfunction Syndrome Uncontrolled metabolic acidosis
Chronic organ dysfunction (emphysema, cirrhosis, renal failure)
Prolonged Cardiopulmonary Ressuccitation without adequate tissue perfusion
Compliance (social, cognitive, psychiatric or financial limitations)

of the physiological aspects, this subgroup has decreased and has been overtaken by the older post-surgical patient subgroups.

On fulfillment of the above criteria, patients with the following [Table 5] neonatal diagnoses are considered for ECMO support.

Extracorporeal membrane oxygenation in children

Children with congenital heart disease who remain too sick to undergo surgical intervention, or develop worsening of cardiac failure in the postoperative period with maximal ionotropic support, or have outgrown the ability of their reconstructed heart to function, form the major group of patients requiring ECMO support [Table 6]. In these children the mechanisms of compensation are stretched to the maximum limit and adequate gas exchange can only be maintained through adequate tissue perfusion using extracorporeal support.[4-6]

Additionally, cardiac failure can result from non-congenital medical conditions such as viral myocarditis or cardiomyopathies, which are reversible. For these diverse groups of patients, ECMO is often the only option for short-term cardiac support while waiting for either native heart recovery or as a bridge to transplantation. Under these circumstances, the advantages of use of ECMO over use of ventricular assist devices (VAD) are:

a. Avoiding open surgery to institute the support.
b. Quick initiation of the support in the ICU or emergency department itself
c. If thoracotomy or sternotomy were to be required at later stages, virgin state of the tissue planes will be an added advantage.[7,8]

Extracorporeal membrane oxygenation in cardiac surgery

ECMO is now considered an important and useful therapeutic modality in children with post-cardiotomy myocardial failure, unresponsive to conventional medical therapies, including optimum preload maintenance, enhancing myocardial contraction and appropriate afterload manipulation. Less commonly, ECMO is used to support it is difficult to wean patients from CPB after cardiac surgery [Table 7]. With an overall increase in experience, early institution of ECMO support has been emphasized to reduce cardiac arrest, end organ damage, and failure to wean from CPB, resulting in better patient outcome. It was recently shown that when used as a bridge to surgery, ECMO represented a useful modality to rescue pateints with failing circulation and irreparable complex heart defects.[7,8]

Whenever ECMO support is required in children either prior to or after cardiac surgery, a search should be made to diagnose residual heart defects as early as possible, since carrying out interventions to rectify these defects may prove crucial for patient survival. Early diagnosis using echocardiography and/ or cardiac catheterization may be recommended to achieve the above goals. Other less common indications include the support during interventional cardiac catheterization procedure for a hemodynamically unstable patient.[9]

Extracorporeal cardiopulmonary support in adult patients

(1) Acute respiratory distress syndrome (ARDS) with secondary lung injury (following shock, trauma,

Table 4: ECMO consideration criteria exclusively for neonates

Oxygen Index > 40
No major cardiac defect
Absent fatal chromosomal abnormality
No necrotizing enterocolitis
Reversible lung or cardiac disease
Gestational age > 33 weeks
Intraventricular hemorrhage < Grade II (subependymal and choroid plexus)
No serious bleeding or untreatable coagulopathy

Table 5: Clinical conditions requiring ECMO in neonates/small infants in the first two weeks

Meconium aspiration syndrome
Congenital diaphragmatic hernia
Pneumonia / Sepsis
Group-B streptococcal sepsis
Persistent pulmonary hypertension of newborn
Respiratory distress syndrome
Asphyxia

Table 6: Indications for ECMO in children

Low cardiac output syndrome
Failure to wean off cardiopulmonary bypass
Pulmonary hypertension with circulatory failure
Refractory arrhythmias
Cardiac arrest unresponsive to conventional resuscitation techniques
Respiratory failure
Profound cyanosis due to intra-cardiac shunting
Support for intervention in the catheterization laboratory
Bridge to transplant or assist devices

Table 7: Indications for ECMO in cardiac surgery patients

Cardiogenic shock not responding to maximal intervention
Volume/inotropes/vasoconstrictors
Intra-aortic balloon counterpulsation
Global myocardial failure
Failure to wean from CPB
Temporary bridge to cardiac rest and recovery

sepsis, etc.) – once the patient is on ECMO support for hemodynamic stability, adequate repair of secondary organ damage can be performed. If surgical repair of a malfunctioning organ is required (for example, pancreatic resection and drainage for necrotizing pancreatitis, fasciotomy or amputation for compartment syndromes and gangrene, excision and drainage of abscesses, etc.), the procedure can be adequately performed under ECMO support, without any hemodynamic compromise. Criteria for support are enumerated in Table 8. (2) Pulmonary embolism – when major or massive pulmonary embolism is the cause of respiratory or cardiac failure, venoarterial ECMO institution can be successful, if cannulation and extracorporeal support can be done before the occurrence of any brain injury. (3) Selective CO_2 removal in '*status asthmaticus*' and other conditions with very high blood $PaCO_2$, reducing the blood $PaCO_2$ gradually, to avoid acid–base imbalance or cerebral complications. (4) Support of the tracheobronchial tree during or following surgical repair, to eliminate the need for endotracheal intubation and use of mechanical ventilator support altogether. This may enhance the ease of surgical repair and subsequently facilitate healing without concern for rupturing of the suture lines from applied positive pressure ventilation. (5) Mediastinal masses: Applied in conditions where anterior mediastinal masses cause airway compression with respiratory compromise and where a high risk of death exists, in 'cannot ventilate' and 'cannot intubate' scenarios. During anesthesia induction, ECMO can be electively considered and unlike cardiopulmonary Femorofemoral bypass, ECMO support can be extended into the postoperative support if the situation so demands.[10-14]

Table 8: Criteria for ECMO specific to adults

Cardiorespiratory failure >90% mortality risk
Indication
Failure of conventional medical therapy
Transpulmonary shunt > 30% (FiO_2>60%)
Static compliance <0.5 ml/cm H_2O/Kg
Diffusely abnormal chest roentgenogram. Four quadrants
Cardiac failure or cardiac arrest
Hypercapnea with pH < 7.20
Contraindications
Age > 60 years (relative)
Duration of ventilation > 5 – 7 days
Incurable condition
Intracranial bleed or closed space bleed

FiO_2 - Fractional inspired oxygen concentration

Table 9: Pump types

Occlusive roller pumps
Positive displacement
Resistance-independent
Hemolysis
Constrained vortex pumps
Centrifugally generated pressure differential
Resistance-dependent
Hemolysis in neonates and small infants

ECMO in cardiopulmonary resuscitation

Extracorporeal Cardiopulmonary Resuscitation (E-CPR) has a short-term and long-term survival benefit over conventional CPR in patients with in-hospital cardiac arrest of cardiac origin. This resuscitative method is reasonable for patients suffering from refractory cardiac arrest, who have undergone CPR for more than 10 minutes.[15-17]

Rare conditions requiring extracorporeal membrane oxygenation support

Extracorporeal membrane oxygenation has been used for rare causes of pulmonary failure with variable success in vasculitis, autoimmune lung disease, bronchiolitis obliterans, Goodpasture syndrome, and rare bacterial, fungal or viral infections.[18]

Extracorporeal membrane oxygenation circuit: Component consideration

Pump

Blood pumps with long-term performance are preferred. The servoregulated roller pump is standard in most centers. Many centers use roller pumps [Table 9] and systematically reposition the tubing segment within the pump at regular intervals so that the attrition of the tubing wall, due to the rollers, is distributed over a long distance (Raceway tubing). Other groups use centrifugal pumps and replace the pump heads at regular intervals because of the bearing problems that are related to stagnant blood flow and localized thermal buildup. Centrifugal pumps of more recent design use a single-point sapphire bearing and continuous washing of all rotor and housing surfaces. There are two different types of centrifugal pumps with a center hole in the rotor, which avoids thrombosis and heating: Centrimag (Levitronix) and Rotaflow (Maquet). Both are safe for long-term use.

The new membrane lung can be used with a centrifugal pump if the inlet (suction) pressure does not exceed minus 200 – 300 mm Hg. This negative pressure can occur in seconds if the venous line chatters at high flow, so it should be prevented by keeping the RPM under 3000 and / or by incorporating a compliance chamber in the drainage line (Better Bladder). The advantage of a centrifugal pump is that it cannot blow out at normal

Table 10: Common ECMO oxygenators

Medtronic: Avecor	Medtronic: Minimax/maxima	QuadroxD
Six sizes	Two sizes	One size
Spiral wound silicone membrane	Polypropylene hollow fibers	Polymethylpentene hollow fibers
'True' membrane	'Pseudo' membrane	'True' membrane
	Not used much (short life)	Heat exchanger incorporated

Medos Hi-lite
Three sizes
Hollow fibers
Treated to give plasma seal (lasts many days)
Heat exchanger incorporated

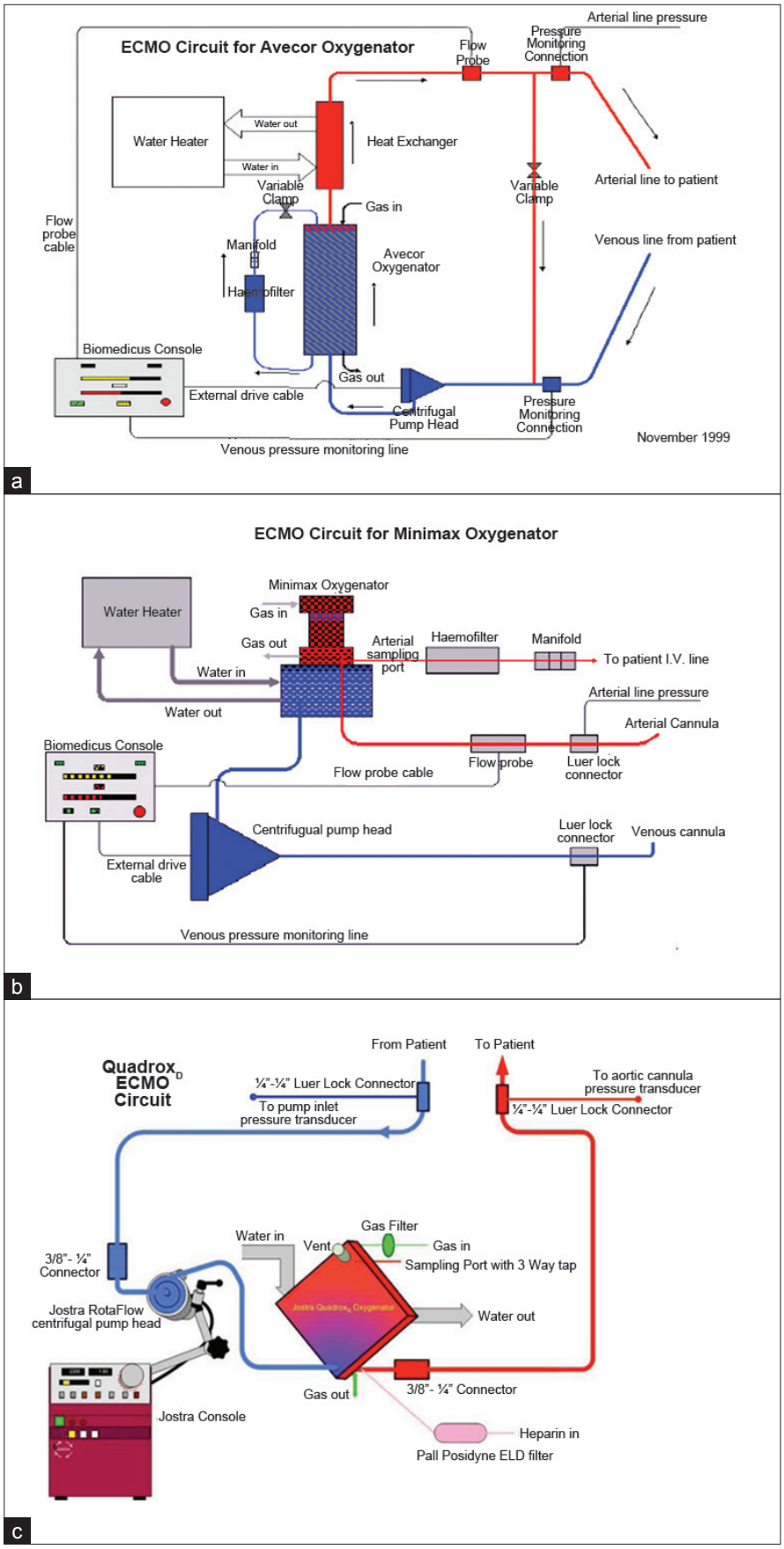
Technical data	Quadrox	Quadrox-D	Avecor 800	Avecor 1500
Blood flow rate	0.5 – 7 L / minute	0.5 – 7 L / minute	1.2 L / minute	1.8 L / minute
Priming volume	250 ml	250 ml	100 ml	175 ml
Effective surface area gas exchange	1.8 m^2	1.8 m^2	0.8 m^2	1.5 m^2
Material	Polypropylene microporous membrane	Polymethylpentene (PMP) microporous membrane	Silicone sheet	Silicone sheet
Effective surface area heat exchange	0.6 m^2	0.6 m^2	Not applicable (heat exchanger separate)	Not applicable (heat exchanger separate)
Material of heat exchange capillary	Polyurethane	Polyurethane	Not applicable (heat exchanger separate)	Not applicable (heat exchanger separate)

	Hi-lite 800LT	Hi-lite 2400LT
Blood flow	800 ml/ minute	2300 ml/ minute
Priming volume	55 ml	99 ml
Surface area	0.33 m^2	0.63 m^2
Pressure drop full flow	45 mmHg	150 mmHg

pressure, even with the arterial line occluded. There is no backflow valve with a centrifugal pump, so the patient can bleed out backwards if the pump stops during venoarterial (VA) ECMO. Also hemolysis in neonates and small infants is clinically more significant, when compared to roller pumps.

Membrane Lung

Membrane lungs are available in a surface area of 0.4 m^2 to 4.5 m^2. The size of the artificial lung is selected to provide total cardiopulmonary support based on the type of oxygenerator and its manufacturer recommendation to the body surface area [Table 10]. The microporous hollow-fiber oxygenators initially used were highly efficient with regard to gas exchange, had low resistance to blood flow, and were also easy to prime. On account of their early failure (plasma wetting and decreased gas exchange), which occurred quickly and unpredictably, use of the spiral wound silicone-membrane oxygenator, Avecor (Affinity, Avecor Cardiovascular Inc., Minneapolis, MN, USA), was popularized over a period of time. Newer developments included microporous hollow-fiber membranes coated with thin siloxane layers to prevent plasma wetting and increase biocompatibility. Poly 2-methoxy-ethylacrylate (PMEA) coatings also resisted plasma leakage and attenuated the inflammatory response, for example, the Medos Hilite 7000LT oxygenator, used a poly-4-methyl-1-pentene (PMP) asymmetric hollow-fiber membrane, also coated with heparin, which had the potential to last for the entire ECMO course. On the other hand, Quadrox D (Maquet Jostra Medizintechnik AG, Hirrlingen, Germany) was a low-resistance nonporous PMP-coated diffusion membrane lung, meant for patients over 10 kg and for smaller patients with a recirculating loop, functioning for a month or more, without need for the regular change out. Although Quadrox D was 'nonporous' and would not leak plasma, there were micro holes that could entrain air, if the pressure on the blood side was lower than the ambient pressure. Therefore, it was essential to keep the lung below the level of the patient. Large patients (over 80 kg) could need two membrane lungs in parallel for adequate gas exchange when there was no native lung function. A new circuit named Permanent Life Support — PLS (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) with the Quadrox D oxygenator had the housing reinforced with glass fibers, to increase the mechanical resistance, and the polyvinyl chloride (PVC) of the circuit was DEHP-free (Bis 2-ethylhexyl-phthalate). On account of these characteristics, this circuit was more biocompatible and had been certified for a support period of at least 14 days. Various oxygenator configurations with ECMO circuits are shown in Figures 2a, b, and c.[19-22]



Figures 2: (a-c) Configuration of circuit for different oxygenators

As can be noted by inspection of the gas outflow port, the membrane is a potent source of insensible fluid loss (water transfer across the membrane is 5 – 10 ml / m^2/ hour at 37^{0}C).

Heat exchanger

The heat exchanger can be separate or be incorporated into the oxygenator [Table 11]. Low pressure flow (3 – 4 Psi) is maintained on the water bath side to ensure that, if any leak which inadvertently occur may cause the blood flow to enter the water bath and not the reverse occurring causing mishap. The counter current mechanism for heat exchange maintains the maximal gradient. The maximum temperature reached is 42°C, to prevent bubble formation or hemolysis due to overheating. It also serves as a last port to catch any air bubbles. For large children and adults the use of the heat exchanger or water bath may not be needed.

Monitors

With the Quadrox D and centrifugal pump little continuous monitoring is needed. Circuit management is driven primarily by the patient's monitored parameters and clinical status. Circuit monitors obtain Inlet – Outlet pressures, blood gases, and saturations intermittently, but can be measured continuously when needed for management. However mixed venous oxygen saturation ($SmvO_2$) is monitored continuously on VA ECMO.

Tubing

With the new system, it is possible to use short tubing (one meter), but longer tubing is needed for prone positioning and trips to computed tomography (CT) or operative suites. Short tubing can be used with ECMO for road trips. Tubing diameter is three-eighth inch for > 30 kg, quarter inch for < 30 kg, and half inch drainage is advised for large adults needing a very high flow.

Bridge

It is a connection between the afferent drainage and the efferent oxygenated circuit tubing. It provides bypass if the patient requires isolation from the circuit without decannulation and the blood flow is constantly maintained in the ECMO circuit to avoid clot formation in case an emergent rerun of ECMO becomes inevitable.

Table 11: Heat exchanger integration with oxygenators

Avecor 0800, 1500	Inserted in the circuit separately
Avecor 2500, 3500	Integral with the body of the oxygenator
Jostra QuadroxD, Medtronic Minimax and Maxima	Incorporated in the body of the oxygenator

During the ECMO run, unclamping at every 15 minutes is done to ensure patency of the line, or alternatively, a flow constrictor is used.

Bladder

Silastic bladder with a capacity of 35 ml is placed at the lowest point on the venous side. The ECMO circuit contains a relatively fixed volume of blood, with the silicone bladder being the only element of volume variability. The volume cannot be transferred from a patient to a component in an ECMO circuit, as can be done with a reservoir in an operative bypass circuit. The patient is the only compliant component of the ECMO circuit, and excess volume in this closed system is seen as third-space edema and intravascular volume expansion in the patient. Reduction in the total fluid requires diuresis, hemofiltration or actually removing blood from the circuit. The bladder is housed in bladder box, which has a feedback sensor or a proximity switch attached to its top surface that acts to regulate the roller pump by turning it off in case of a bladder collapse from impaired return or hypovolemia, thereby preventing 'cavitation' (gas coming out of solution and forming bubbles) created by negative pressure in the circuit.

Heparin-coated circuits

Heparin surface coatings have been shown to improve thromboresistance of the blood-exposed surfaces of the circulatory support devices, and to allow reducing systemic anticoagulation, with subsequent reduction in any bleeding complication. Furthermore, heparin surface coating can also be applied to proof gas exchangers with true membranes. However, the thromboresistance of heparin surface coating is dependent on the blood flow and can be reduced by avoiding the use of protamine to reverse the systemic anticoagulation.[23-31]

Integrated extracorporeal membrane oxygenation circuit

This indigenous redesign [Figures 3a and b] of the venoarterial ECMO is done in our institution for extending the boundaries of primary Arterial Switch Operations (ASO) in the Transposition of Great Arteries with intact ventricular septum beyond three weeks. The circuit can also be used for obstructed Total Anomalous Pulmonary Venous Connection (TAPVC), Anomalous Left Coronary Artery from Pulmonary Artery (ALCAPA) for preoperative and postoperative support, including performance of surgery on the ECMO circuit. Table 12 enumerates the advantages of the integrated ECMO circuit.[32]

The two parallel circuits of ECMO and CPB are integrated at the level of the membrane oxygenator (MO) and the

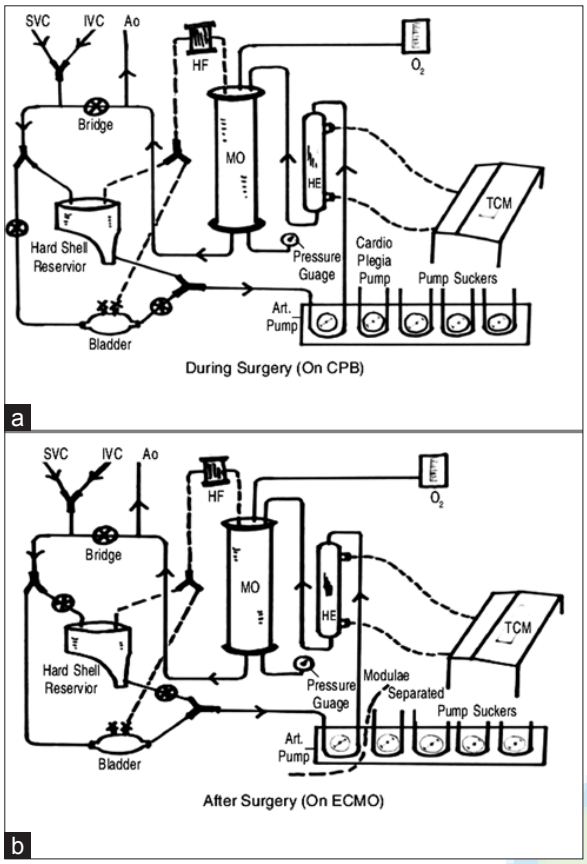


Figure 3: (a and b) Integrated ECMO Circuit, SVC - Superior vena cava, IVC - Inferior Vena Cava, Ao - Aorta, HF - Hemofilter, MO - Membrane Oxygenator, HE - Heat exchanger, TCM - Temperature control machine, CPB - Cardiopulmonary Bypass, ECMO - Extracorporeal membrane oxygenation

heat exchanger. During surgery (on CPB), the 'hard shell' non-collapsible cardiotomy reservoir is used; and after surgery (on ECMO), the collapsible soft reservoir 'bladder' of the ECMO is used. The entire assembling is performed prior to the initiation of surgery.[33]

The safety features of the ECMO circuit are shown in Table 13.

Technical considerations

Priming of the circuit

Using a pre-connected circuit, flushing with 100% CO_2 is done, followed by antegrade priming and debubbling. Red cells are added to get the hematocrit to 0.4 with 100 – 150 units of heparin in prime. Sweep gas flow is set to one-tenth of the basal flow, with FiO_2 of 21%, and a buffer is added to the prime to normalize the base. The transonic flow meter should be zeroed at this point. Recirculation of prime is done with 1000 ml / minute flow for < 20 kg patients and with 4000 ml / minute flow for > 20 kg patients. The final prime potassium level in the prime is checked carefully and the ionized calcium is corrected along with the check

Table 12: Advantages of integrated ECMO

Advantages of Integrated ECMO
Incorporated CPB circuit
Increased preparedness with availability of ECMO
Cut-down assembly time
Reduced possibility of CPR and E-CPR
Cost-effective

CPB - Cardiopulmonary Bypass, CPR - Cardiopulmonary Resuscitation, E-CPR - Extracorporeal CPR

Table 13: Various safety features incorporated in the ECMO circuit

Venous bladder and pump controller
Bridge
Mixed Venous O_2 saturation monitor
Transonic flow meter
Pressure alarms
Bubble detectors
Battery backup (supplementary electrical supply on the ECMO trolley)

Table 14: Anticoagulation maintenance

Cannulation – Heparin 75 – 150 IU / kg ACT > 300
(Heparin in prime 40 – 100IU/Ltr.)
Maintenance – Heparin infusion 25–50 IU / kg / hour
Target ACT 180 – 240s
ACT > 300s – withhold infusion
ACT > 280s – risk of bleeding
– reduce infusion by 2.5 – 5 IU / kg / hour
ACT < 160s risk of thrombosis – repeat bolus heparin

ACT - Activated clotting time

of all safety devices and alarms, prior to the ECMO run. The volume of the neonatal circuit is approximately 400 – 500 mL, which is one to two times the newborn blood volume. The circuit, therefore, must be primed carefully, so that the neonate at the initiation of bypass is perfused with blood containing the appropriate pH, hematocrit, calcium, clotting factors, electrolytes, and temperature. However, ECMO may be instituted in those patients over 35 kg in weight without the addition of blood in the prime.

Anticoagulation

Heparin must be administered before cannulation. A loading dose of 100 units / kg is administered to the patient two minutes before cannulation and at the surgeon's request. If ECMO is not commenced within 15 minutes an additional single dose is considered based on activated clotting time (ACT) [Table 14].

Cannulation

Access for ECMO is provided via extrathoracic cannulation in general and the transthoracic cannulation approach is followed in the post-cardiac surgery patient with cardiac and / or pulmonary dysfunction. Appropriate positioning for cannula placement should be ascertained only after proper securement of the

endotracheal tube. The patient should be positioned in anti- Trendelenberg position with the head turned away from the site of cannulation. Availability of blood or albumin at the bedside is emphasized and made available at hand in case there is any event of blood loss or volume resuscitation crisis. All infusion lines must be accessible (not lost under the drapes), with blood and volume expanders connected, for any emergent administration (if the situation so demands). Anesthesia includes narcotics for pain and neuromuscular blockers for immobility during cannulation. Venovenous (VV) ECMO is preferred over venoarterial (VA) ECMO whenever possible, because isolation, cannulation, and ligation of the carotid artery is avoided. In infants and neonates, pressure is applied on the liver during venous cannulation, to ensure that the flow of blood remains out of the cannula with avoidance of air embolism. A cephalic cannula in the jugular vein can monitor jugular mixed oxygen saturation, augment venous drainage, decrease venous congestion, and decrease intracranial hemorrhagic episodes.[34] During carotid artery isolation and cannulation, bradycardia and hypotension may result from the close proximity of the vagus nerve in the carotid sheath. Factors such as neck hyperextension and lung inflation at the time of cannulation are to be considered for assessing the correct depth of catheter insertion in the chest radiogram.

For adults, the size of the intravascular catheters may be 20 Fr or larger, while 14 Fr catheters may be used in infants. These are generally placed by cut-down. The following should be seen as a guide [Tables 15 – 18] [Figure 4] rather than an absolute indication of the size for cannula selection. As a rule, whenever the venous drainage is good, more satisfactory level of ECMO support is achieved, thus choosing a relatively larger sized cannula seems attractive. The placement of an extra-venous cannula might be necessary with the evidence of inadequate return and the possibility of such a situation occuring should be borne in mind.[35]

Initiation of extracorporeal membrane oxygenation

Initiation of ECMO is done at flows of 20 ml / kg / minute, by first unclamping the arterial or oxygenated line, followed by clamping of the bridge and unclamping of the venous line. The flow is gradually increased to 100 – 150 ml / kg / minute over 10 – 20 minutes, or to the desired flow with minimum RPM, to minimize cardiovascular changes, in accordance with the assessment of the total obtainable blood flow. The full flow must not only satisfy the criteria of warmth, perfusion pressure, and oxygen delivery, but must also be adequate to reduce cardiac filling and distention. Cardiac ejection must not occur unless there is an attempt to assess myocardial function or a trial to wean from cardiac support ECMO.

Table 15: ARTERIAL cannula size guide

Flow (ml/minute)	Size (Fr)	External diameter (mm)
0 to 400	8	2.66
400-700	10	3.33
700-1200	12	4
1200-1700	14	4.66
1700-2000	15	5
2000-2500	17	5.66
2500-3500	19	6.33
>3500	21	7

Table 16: VENOUS cannula size guide

Flow (ml/minute)	Size (Fr)	External diameter (mm)
0 to 350	8	2.66
350-600	10	3.33
600-1000	12	4
1000-1400	14	4.66
750-1000	15	5
1000-1500	17	5.66
1500-23000	19	6.33
2000-2500	21	7
25000-5000	23	7.66
3000-3600<	25	8.33
3600-4500	27	9
4500<	29	9.66

Table 17: Pump flows

Neonates	150 ml/minute×bodyweight
Pediatric up to 10 kg	100-150 ml/minute × bodyweight
Pediatric - >10 kg	2400 ml/m^2/minute × body surface area (BSA)
Adults	2400 ml/m^2/minute × BSA

Table 18: Sizes of Origen Venovenous cannula (OriGen Biomedical Inc. Austin, TX USA)

12 Fr for children 2-5 kg
15 Fr for children 4-8 kg
18 Fr for children 7-12 kg

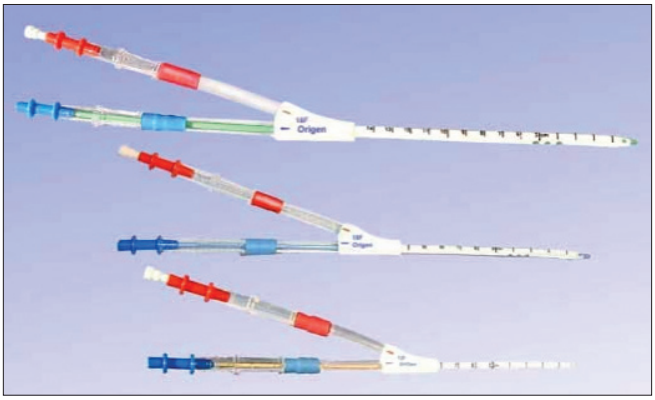


Figure 4: OriGen Veno-venous cannula in three sizes

Inotropes are gradually tapered off. Minimal inotropes are used during cardiac support ECMO. Hypertension is aggressively treated with vasodilators. In neonates a perfusion pressure of 40 – 55 mmHg is targeted. High flows can cause hypertension. Weaning onto support is done very slowly to allow gradual mixing of the prime with the patient blood, as there may be a large difference in volume between the patient and the ECMO circuit. The gas flow is started at the desired blood flow (1 : 1). The gas inlet pressure must be monitored, as a sudden increase can cause the oxygenator membrane to rupture. The ideal gas inlet pressure is < 50 mmHg. A pump inlet pressure monitoring line is attached to the venous cannula connector. This line must be flushed regularly to prevent it from clotting as it monitors the patient volume status and change in cannula position.

Monitoring on extracorporeal membrane oxygenation

(Table 19) Once the patient is stabilized, the pump flows may be decreased to keep the PaO_2 in the 85 – 100 mmHg range. The patient must have an adequate circulating blood volume to obtain good flow rates. Blood sampling may average 50 ml per day in the neonate on ECMO. Blood may also be lost from the cannulation sites. Careful and complete fluid balance demands hourly monitoring. Decision on volume replacement depends on the hemoglobin (Hb), platelets, and blood or plasma protein levels. Packed red cells are given if the Hb drops below 9 g / dl, fresh frozen plasma or albumin is given if the Hb is above 9 g / dl, and platelets are given if the platelet count is less than 50,000. Transfusion of antithrombin III (AT III) is required if the AT III serum level falls below 80%. Sodium citrate preservative in the donor blood binds with the ionized calcium; therefore, calcium gluconate or calcium chloride is usually administered with each 100 ml of blood or plasma. Total serum and ionized calcium levels should be monitored every eight hours. The size of the arterial cannula contributes to the resistance in the circuit, as it does in CBP. Hemolysis can occur with a high flow, through narrow orifices, so the larger the cannula the more the chances of less hemolysis occurring. This is more critical than with the conventional CPB because of the time period with support on ECMO.

Table 19: Monitoring parameters on ECMO

Time	Parameters
Hourly	Activated Clotting Time
	Urine output
	Ventilator settings
	Invasive BP, HR, CVP
	Temperature
	(avoid rectal temperature monitoring, may cause mucosal bleed)
	SaO_2 (continuously) - Pulse oxymeter and Oxysat in line
	$SmvO_2$ (continuously) - Oxysat in line
	Negative pressure in venous line
	0-40 mmHg in Pediatrics
	0-80 mmHg in Adults
	Pressure before oxygenator
	Pressure after oxygenator
	Temperature patient / heat exchanger
	% O_2 on Mixture
As and when required	Arterial blood gas – oxygenator and arterial line
	Serum electrolytes
	Hemoglobin
	Hematocrit
	Ultrasound-Caput/abdomen in newborn (bleed in closed space)
	Cardiac (PDA/suspected residual defects/shunts)
	Cannula position
	Chest X-Ray
Daily	Hemolysis tests - Plasma free hemoglobin,
	Electrolytes - routine and P. Mg, Ca (ionized)
	Urine Electrolytes
	Coagulation status including Antithrombin III
	Hemoglobin
	Hematocrit
	Platelets
	Total and differential leukocyte counts
	C-reactive protein
	Ultrasound - Caput / abdomen in newborn
	Cardiac (ductus arteriosus shunt)
	Cannula position

BP - Blood pressure, HR - Heart rate, CVP - Central venous pressure, PDA - Patent ductus arteriosus, SaO_2 - Arterial oxygen saturation, $SmvO_2$ - Mixed venous oxygen saturation

Sampling sites on the extracorporeal membrane oxygenation circuit

All blood samples other than the patient's arterial blood gas are obtained from the ECMO circuit. The samples are drawn from the first pigtail after the bridge on the venous side and prior to the bladder for ACT and for all biochemistry parameters. For blood gas sampling on the circuit: (1) A venous gas sample is taken before the blood reaches the bladder and it measures the blood gases from the blood returning to the machine from the patient. (2) A post-membrane gas sample is taken from the pigtail after the oxygenator, and is used to assess the oxygen and carbon dioxide exchanging function of the membrane. On ECMO this should be checked every 12 hours for oxygenator failure.[18]

Clinical Considerations *Ventilator and lung management*

Ventilation is kept at a low settings [Table 20] aiming at lung rest (target - PPlat under 25 cm H_2O, FiO_2 under 0.4). There will be some blood still flowing in the lungs and it is important that it is oxygenated, as this will

Table 20: Ventilator settings for complete lung rest

Tidal volume of 6–8 ml kg/liter
Rate of 10–12 breaths / minute
Positive end-expiratory pressure (PEEP) of 6–10 cm H_2O
(High PEEP>10 cm H_2O – avoided to prevent suppression of cardiac diastolic function)
The peak airway pressure maintained at <35 cm H_2O, to avoid barotrauma
$PaCO_2$ maintained within the normal range to prevent organ damage
FiO_2 (Fraction of inspiratory oxygen) of 40–60%
ECMO flow of at least 0.6 liter/minute

minimize the admixture of the desaturated blood from the pulmonary circulation joining the fully oxygenated blood from the ECMO circuit. If an expected long run is anticipated, an early tracheostomy will facilitate all aspects of care, including facilitation of minimal sedation. These patients often have bleeding from the lung parenchyma and it may necessitate frequent tracheobronchial suctioning and lavage. Hemoptysis should not be considered as a sign of futility and must be managed as any bleeding complication. High-frequency oscillatory ventilation can be used at rest settings (mean airway pressure 12 – 14 cm H_2O), and may help with recruitment. Until there is some sign of lung recovery, there is no indication for recruitment maneuvers, or other ventilation devices or maneuvers. Infants and neonates must receive four doses of surfactant 100 mg / kg. When there is some native gas exchange and aeration, it is reasonable to begin the recruitment maneuver, (prolonged inspiration at 25 cm H_2O). The use of adjunctive measures such as nitric oxide, surfactant, prone positioning, fluorocarbon lavage, and percussive ventilation have been reported to be helpful in recruitment in some centers. Chest CT showing posterior consolidation is only an indication for prone positioning, which will recruit posterior lung units when recovery begins and is evident on respiratory support with ECMO.[36-38]

Other organ systems

Skin and general care for pressure points and invasive lines should be taken to prevent skin trauma and breakdown. Antibiotic prophylaxis and treatment are to be administered as per the institution's protocol. Avoid nasopharyngeal suction, venepuncture, lumbar punctures, and elective invasive interventions on the ECMO run, unless it is an emergency.

Fluid and electrolyte imbalances: Extracellular fluids increase by about 30% and paradoxically water loss occurs from membrane oxygenators. An edematous state is common and electrolyte requirements are increased due to higher circuit volumes. Standard parenteral or enteric nutrition for age is carefully implemented, considering that these fluids shift to avoid circulatory overload.

Central Nervous System: Impaired venous drainage due to venous cannulation of the internal jugular veins, with additional risks of thrombosis or bleed, remains the major cause of morbidity and mortality. Reperfusion injury with cerebral edema can further compound these problems. Serial ultrasounds are done daily, in infants, to screen for bleeding complications, which preclude further ECMO runs.

The Hepatobiliary System: Indirect hyperbilirubinemia secondary to hemolysis and direct bilirubinemia secondary to cholestatic jaundice occur often.

Renal System: Oliguria and associated renal dysfunction are worsened on ECMO. Continuous veno-venous hemofiltration is a helpful adjunct to decrease the biochemical load.

Weaning or trial period without extracorporeal membrane oxygenation

In patients with a principal pre-ECMO diagnosis of respiratory failure, weaning trials are not indicated till substantial signs suggestive of native lung recovery are seen. Most ECMO centers are not accustomed to 30- to 60-day runs, but even total fibrosis, when documented, has been reversible. Even though there are acute respiratory distress syndrome (ARDS) survivors after a month (the longest is 120 days), the utilization of the ICU and ECMO resources is a consideration. At present the best indicator of irreversible lung fibrosis is the PA pressure and evidence of right ventricular failure (although some patients have recovered with longer VA support). The trial period without ECMO is scheduled if (1) the patient demonstrates adequate gas exchange and is on reasonable ventilator settings, and (2) the patient tolerates a pump flow of 10 – 20 ml / kg / minute with a minimum of 200 ml / minute. Inotropes are optimized to pre-ECMO levels and the pump flow is decreased to 20 – 50 ml every 20 – 30 minutes, as long as the mean arterial pressure, CVP, and $SmvO_2$ are maintained within the prescribed limits. To avoid hypocarbia during weaning, the sweep must be reduced at the same rate as the blood flow. Ensure a post-oxygenator gas check should hypoxia occur. Once the flow has reached 100 ml / minute or 30 ml / kg / minute, weaning is stopped and the flow reassessed. Decannulation is done two to four hours after clamping off and requires anesthesia, positioning, and equipment, as for cannulation.

Assessment for the failure to wean from ECMO

- Lung recovery inadequate or irreversible
- Cardiac recovery inadequate or irreversible
- Ionotropic optimization mismatch
- Ongoing infection
- Pulmonary hypertension
- Pulmonary complications - pneumothorax/bleed/ abnormal lung
- Circuit issues - calibration/inaccurate measurement/ cannula obstructing aorta

Indications for hemofiltration

Ideally, the ECMO circuit should not be accessed for hemofiltration. The poly-methyl pentene (PMP) oxygenators have a very low pressure drop across the membrane, and therefore, it is unsuitable to operate a hemofilter in a parallel circuit with the oxygenator. As many of these patients will be in renal failure, it is imperative to have a low threshold for continuous renal replacement therapy (CRRT). Hemofiltration is used on ECMO [Table 21] for managing oliguria or anuria with fluid retention (resistant to high-dose diuretics), edema, electrolyte balance, for removing blood-borne toxins, and the administration of full-volume nutrition and blood products, without fluid overload. Hemofiltration must be set up separately if possible, however, if required, the safest option is to withdraw blood from the arterial side of the circuit and return it to the venous side through the port at the bottom of the oxygenator. The shunt through the hemofilter steals a proportion of the pump flow (between 10 and 20%, depending on the way the filter is connected) and reduces the net flow to the patient. Slow continuous ultrafiltration (SCUF) can remove up to 10 ml / kg / hour, and with continuous arterial-venous hemofiltration (CAVH) up to 50 ml / kg/ hour of filtrate.

Transfer on extracorporeal membrane oxygenation

Patients may require transfer for investigations (CT scan/ angiography), interventions in hybrid surgical suits, or to different higher referral centers. Prior to shifting clotting profiles, electrolyte, and volume status has to be optimized. Sedation and neuromuscular blockade may be required at times. Care of circuits and cannulas during shifting and availability of extra oxygen, battery packs, manual cranks, extra blood, and volume expanders, depending on the length of transfer or transport, are among the areas of impending potential complications [Table 22].[39]

Invasive procedures on extracorporeal membrane oxygenation

Any invasive procedure is associated with increased risk of mortality and bleed, secondary to anticoagulation.

Table 21: Indications for hemofiltration

Fluid overload - non-responsive to high doses of diuretics
Parenteral nutrition restricted because of fluid limitations
Prevention of hyperkalemia or azotemia
Impaired pulmonary diffusion with circulatory failure
Hypernatremia - unresponsive to natriuretic drugs

Table 22: Complications noted on ECMO transfer

Power failure
Circuit tubing leakage
Circuit rupture
Membrane lung thrombosis
Hypocapnia/hypoventilation

Table 23: Required hematocrit and clotting screen prior to invasive procedures

ACT 160-180 seconds
Platelets >100,000/cumm
Fibrinogen >150-300 mg/dl
Anti-thrombin 380-120% of control
Hematocrit~40%

Prior to the procedure, clotting screen and total platelet counts with hematocrit are optimized [Table 23]. Chest drain insertion, central lines, arterial lines, reintubation, septectomy, septostomy, angiogram, transesophageal echocardiography, bronchoscopy, and pericardial tap are among the invasive procedures demanded on ECMO.

Unless in an absolute emergency or an effect on flow dynamics being the issue, chest drain insertion necessitated for pneumothorax or pleural effusion may be left initially undrained, and thus, can be monitored until the patient is weaned from the ECMO. Factor VII administration is considered if bleeding exceeds 10 ml/ kg / hour post the procedure.

Complications associated with extracorporeal membrane oxygenation

Known hazards of the ECMO technique can be classified into mechanical and patient medical complications [Table 24]. Mechanical complications include oxygenator failure, tubing / circuit disruption, pump or heat exchanger malfunction and problems associated with cannula placement or removal. Patient-related medical problems are bleeding, neurological complications, additional organ failure (renal, cardiovascular or hepatobiliary, etc.), barotrauma, infection, and metabolic disorders.

Urgent discontinuation of extracorporeal membrane oxygenation

Emergency conditions [Table 25] require urgent discontinuation of ECMO, with the return of ventilatory

Table 24: Complications on ECMO

Mechanical circuit complications	Patient complications
Cannula and tubing	Renal
Wrong size	Capillary leak syndrome
Bleeding	Loss of auto regulation
Malposition	Fluid retention
Clotting	Hematological
Dissection	Hemolysis'
Decannulation	Thrombo-occlusive disorders
Bladder	Coagulopathy
Inadequate return	Neurological
Hypovolemia	Intracranial bleed
Increased intra-thoracic pressure	Sinus thrombosis
Venous cannula occlusion	Cerebral Infarction
Capillary leak Syndrome	Seizures
Air embolism	Cardiovascular
High FiO_2	Myocardial stunning
Inlet obstruction	Sub-endocardial ischemia
Gas - blood leak	Poor capillary refilling
Pump	Hypoxia re-perfusion injury
Pump failure	Pulmonary
Loss of occlusion	Pulmonary fibrosis
Oxygenator -	Pneumonitis
Thrombosis – Membrane/Inlet/	Consolidation
Outlet port	Pulmonary hypertension
Fluid in Gas phase	
Failing oxygenator -	
Decreased O_2/CO_2 transfer	
Widened pre- and post-membrane gradient	
Increased hemolysis	
Coagulopathy	
Heat exchanger	
Corrosion and leak	
Hemolysis, dilution and electrolyte imbalance	
Sepsis	
Hyponatremia, Hemolysis and seizures	

Table 25: Emergency situations necessitating urgent discontinuation of ECMO

Accidental decannulation
Gross hemorrhage around the cannula
Circuit rupture or rapid leak of blood
Air in the circuit between the oxygenator and the patient

Overall Patient Outcomes

	Total	Surv ECLS		Surv to DC	
Neonatal					
Respiratory	23,558	19,964	85%	17,720	75%
Cardiac	3,909	2,338	60%	1,515	39%
ECPR	537	340	63%	203	38%
Pediatric					
Respiratory	4,376	2,831	65%	2,431	56%
Cardiac	4,776	2,995	63%	2,250	47%
ECPR	1,003	528	53%	387	39%
Adult					
Respiratory	1,860	1,140	61%	968	52%
Cardiac	1,131	541	48%	379	34%
ECPR	406	147	36%	109	27%
Total	41,558	30,824	74%	25,962	62%

ELSO Registry, 2010.

Figure 5: Patient outcome as per extracorporeal life support organisation (ELSO) 2010 registry. (Courtesy Curtis Froehlich), Surv ECLS - Survival on extra corporeal life support, Surv to DC - Survival to discharge

support to pre-ECMO settings or initialization of hand ventilation, and also necessitates the stopping of all infusions going to the ECMO circuit. All infusions including inotropes and total parental nutrition are reattached to the patient. Clamping the patient's venous or arterial cannula depending on the situation with the underlying crisis, and finally unclamping of the bridge is done. Turning off the gas flow to the membrane will prevent super-saturation. Till the rectification of the snag, possible recirculation of ECMO blood at 200 ml / minute is attempted.

EVALUATION OF THE OUTCOME

Extracorporeal membrane oxygenation is a difficult therapy to study and compare with the conventional means of support. The other problem with the studies on ECMO for adult patients is that there are very few patients who are sick enough to need ECMO with reversible disease allowing ethical randomization for alternative theraputic comparison studies. Less than 20% of the ARDS deaths are caused by respiratory failure, while higher numbers of pediatric and neonatal deaths are caused by primary respiratory failure, which explains the greater success of ECMO in pediatrics than in adult medicine. Infants with meconium aspiration syndrome had a 93% survival rate, while patients with congenital diaphragmatic hernia had the lowest survival rate, at 62%. Adult patients for severe respiratory failure complications were not infrequent and were associated with reduced survival; however, overall survival to discharge was 50%. Unmatched patients who underwent extracorporeal–CPR (E-CPR) had a higher survival rate to discharge and a better one-year survival than those who received conventional CPR. Between the propensity-score-matched groups, there was still a significant difference in survival to discharge, favoring E-CPR over conventional CPR. In pediatric patients who had undergone cardiac surgery, survival rates as high as 50% were achieved by implementing ECMO prior to the occurrence of multiple organ failure, in smaller children. The overall survival rate on ECMO as a bridge to recovery and transplantation has been 54.5%, with successful hospital discharge of patients. Overall patient outcomes from the Extracorporeal Life Support Organization (ELSO) 2010 registry, are summarized in a tabular format, courtesy Curtis Froehlich, and shown in Figure 5.[40-41]

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