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THE STATE OF THE ART IN EXTRA CORPOREAL MEMBRANE OXYGENATION

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ABSTRACT

Extra corporeal membrane oxygenation (ECMO) has evolved in design, technology, patient selection, insertion techniques, adjunct devices and management in the past 45 years since it began. Outcomes have improved and indications have expanded. It remains an expeditious, cost-effective tool for rapid resuscitation of patients with cardiorespiratory failure, whose outcomes without ECMO intervention are predominately fatal. However, results are still guarded and the ethical aspects of ongoing care needs to be at the forefront of daily family discussions, in those where a bridge to transplant or definitive device are not possible.

KEY WORDS
Extra corporeal membrane oxygenation, extra corporeal life support, respiratory failure, cardiorespiratory failure
INTRODUCTION

Extracorporeal membrane oxygenation (ECMO), often referred to as extra corporeal life support (ECLS), provides temporary support to critically ill patients who cannot maintain their respiratory and/or circulatory function. A basic circuit composed of cannula, tubing, a pump, oxygenator and heat-exchanger; there are two approaches: veno-venous (VV) ECMO for solely respiratory support, and veno-arterial (VA) ECMO for cardiac support, cardio-respiratory support, or undifferentiated etiology support. Since first use in 1971\(^1\), ECMO circuits have improved in design and function\(^2\text{-}^4\). This review focuses on the current trends in patient selection, improvements in insertion techniques and contemporary management considerations, which have improved clinical outcomes.

EVOLUTION TO CONTEMPORARY ECMO

Gibbon’s development of the heart-lung machine facilitated the first open heart surgery in 1953\(^5\). Initial use of heart lung machine was restricted to the operating room because of damage to blood due to direct exposure to oxygen. The advent of spiral coil type membrane oxygenators, circumvented this concern, and lead to the first experiences with maiden ECMO circuits in the early 1970s\(^1\). Initial experience was for acute respiratory distress syndrome (ARDS), with the early experience of ECMO predominantly reported in pediatric cohorts\(^6\text{-}^7\). Growing interest in ECMO led to a National Institute for Health (NIH) funded multicenter randomized controlled trial, the first of its kind comparing ECMO to conventional mechanical ventilation for ARDS. While no survival benefit was discerned, with poor survival in both groups, interest in ECMO waned\(^8\).
As heart-lung machine technology continued to develop in the operating rooms as cardiac surgery developed, this improved technology became applied to future iteration ECMO circuits with favorable results. Centrifugal pumps have replaced early rotor pumps in contemporary ECMO circuits\(^2\), reducing hemolysis and improving flow dynamics. New biocompatible surfaces\(^9\) such as heparin coated circuits allow reductions in systemic anticoagulation, potentially reducing incidence of bleeding events and systemic inflammatory response syndrome (SIRS). Innovations leading to the development of solid hollow fiber membranes\(^3,4\) resulted in reduced incidence of air embolism and blood trauma due to oxygen exposure. Smaller and portable configurations facilitated VA ECMO as a tool to initiate management of patients in less intensive settings and enable ease of transport\(^10\) to advanced care centers (e.g. Cardiohelp\(^{\text{TM}}\) device, Maquet). Newer duel lumen cannula\(^11,12\) (e.g. Avalon\(^{\text{TM}}\), Maquet; and TandemHeart\(^{\text{TM}}\) Right Ventricular Assist Device cannula with oxygenator) have made it possible to provide VV ECMO respiratory support with single cannula, peripheral inserted in the internal jugular vein via Seldinger technique.

Currently, ECMO is utilized for not only pulmonary and circulatory failure, but for transport, retrieval of organs and extracorporeal CPR. Most recent data from the Extracorporeal Life Support Organization (ELSO)\(^13\) illustrated more than 14,000 patients have utilized short or medium term ECMO support, with high overall survival to discharge, ~60% in respiratory and ~45% in cardiac failure.

**INDICATIONS**

The use of ECMO is often considered in critically ill patients, and often indicated when the pre-ECMO mortality exceeds 80%\(^14\). Contraindications include cerebral hemorrhage due to the need for anticoagulation, severe immunosuppression due to SIRS, or terminal diagnosis.
**Veno-arterial ECMO**

VA ECMO is one of many options available for circulatory support. Other options being various ventricular assist devices both surgically implanted and percutaneous. The distinction with VA ECMO compared with these includes ease of emergent insertion, potential for biventricular support and ability to provide respiratory support. It may be used as a bridge to myocardial recovery, heart transplantation or permanent ventricular assist device.

Potential indications for VA ECMO include spectrum of both isolated cardiac failure as well combined cardiorespiratory with objective evidence of poor tissue perfusion despite optimal intervention. VA ECMO is most commonly employed in setting of cardiogenic shock due to variety of etiologies, such as post myocardial infarction, fulminant myocarditis, peripartum cardiomyopathy, septic shock causing cardiac depression, decompensated heart failure, and most commonly, post-cardiotomy shock (failure to wean off cardiopulmonary bypass), as examples.

Recent novel yet less common indications for VA ECMO support include: extracorporeal cardiopulmonary resuscitation (eCPR), resuscitation in cases of severe hypothermia, and extracorporeal interval support for organ retrieval (EISOR).

**Veno-venous ECMO**

VV ECMO provides respiratory support; indicated in patients with severe hypoxia or hypercapnia due to poor lung function. Objective parameters in ELSO guidelines suggests VV ECMO with PaO$_2$/FiO$_2$ ratio of <150 and/or Murray Score of 2-3 and strongly indicates it when PaO$_2$/FiO$_2$ ratio drops below 80 or with Murray Score of 3-4. Additional consideration for VV ECMO include: severe hypoxemia (PaO$_2$/FiO$_2$ < 80) with high PEEP (typically 15-20 cm of H$_2$O) and potentially reversible pulmonary function, severe hypercapnia with arterial pH <7.15
despite optimal mechanical ventilation, or plateau airway pressure of 35-40 cm of H₂O despite optimal mechanical ventilation.

In clinical scenarios, VV ECMO is most widely used in cases of severe ARDS when lung protective ventilation protocols fail. It can also be employed in severe respiratory failure caused by various etiologies such as: acute lung injury, COPD, severe asthmatic attacks or severe influenza (e.g. H1N1). VV ECMO can also be used to allow recovery time for allograft in cases of primary rejection in lung transplant. It can also be employed as bridge to lung transplant for acute decompensated cases with temporary support requirement.

The only instance where VV ECMO can be used to support cardiac failure is in cases of right ventricular failure secondary to pulmonary vasoconstriction, where there is potential to reverse pulmonary vascular resistance by improving oxygenation and CO₂ removal.

TECHNICAL CONSIDERATIONS

Veno-arterial ECMO

VA ECMO support can be initiated via intrathoracic or peripheral cannulation. Intrathoracic cannulation is usually performed after open-heart surgery (post-cardiotomy shock) or to solve peripheral ECMO complications. The venous cannula is placed in the right atrium. This siphons blood volume from body and acts as the inflow to the ECMO circuit, which subsequently contains the oxygenators and heat-exchanger in series. The outflow from the ECMO goes into an arterial cannula, which is placed in the ascending aorta. Both cannulas can be tunneled through the skin to allow a definite chest closure and potential patient extubation.
For peripheral cannulation the femoral vein is the preferred venous line. The venous cannula is placed in the right atrium through the femoral vein, also using Seldinger technique\textsuperscript{17}. The arterial line can be placed in the femoral artery, axillary artery or even in the carotid artery as in the pediatric population. In all cases, cannula insertion can be totally percutaneous, in which case, a short arterial cannula is positioned distally to prevent distal ischemia\textsuperscript{18}. The completely percutaneous access is the desired one in emergency cases as it allows start support in minutes. However, a surgical cutdown and sewing a 6-8mm graft onto the vessel and connecting to the ECMO tubing prevents distal arterial bed ischemia\textsuperscript{19-20}. Occasionally, the use of a graft causes hyperperfusion of the corresponding limb. It is more frequent in the axillary artery and can be solved by doing a distal banding of the artery.

**Veno-venous ECMO**

For VV ECMO support peripheral cannulation is the preferable. This can be achieved by a bicaval double lumen cannula that drains non-oxygenated blood from both SVC/IVC and re-infuses oxygenated blood in the right atrium at the level of the tricuspid valve\textsuperscript{11-12} (e.g. Avalon™, Maquet). If this is not available, VV ECMO can be initiated using two cannulas. A femoral cannula position in the IVC would drain the non-oxygenated blood into the ECMO circuit. A short cannula placed in the SVC would be used to infuse oxygenated blood from the ECMO circuit.

All cannulas can be placed using Seldinger technique\textsuperscript{17}, preferably under TEE or fluoroscopy guidance to verify their correct position. In both cases, but especially in the dual cannula system\textsuperscript{21}, repeated assessment of the correct cannula position is fundamental to avoid recirculation.
MANAGEMENT CONSIDERATIONS

Once ECMO support has been started, the goal is to preserve all organs and recover those injured. It is important to obtain a baseline arterial blood gas (ABG) and visceral labs. Daily metabolic panel verifies proper perfusion and oxygenation. Arterial gases and coagulation panels must be obtained hourly, especially on the first hours of support.

Protective ventilation mode should be preferred to allow the recovery if possible. Oxygenator settings (FiO2 and “sweep” [air flow rate]) will be adjusted according to the ABG results. It is important to avoid overcorrection and/or fast correction of pCO2 levels, especially in chronic hypercarbic patient due to the risk of cerebral damage.

Inotropic support and ventricular assist devices (e.g. Impella™, Abiomed; intra-aortic balloon pump; TandemHeart™ trans-septal cannula) should be maintained to facilitate the left-side chamber unloading if cardiac recovery is a possibility.

ECMO flows should be adjusted according to the patient needs. On one hand, flows should be enough to keep a good systemic perfusion measured by urine output, lactic acid levels and mixed venous saturation. On the other hand, ECMO flows should not be high enough to prevent lung circulation. To facilitate lung recovery and avoid development of pulmonary thrombi, at least 0.5 L/min of flows through the lung circulation should be permitted. To enable it, full-flow support should not be maintained for long period of time.

Recirculation

Recirculation is not an uncommon complication in VV ECMO support. It is caused by the drainage of the oxygenated blood that is being infused. As a consequence, the patient remains
hypoxemic despite good ECMO flows. This is avoided by confirming the correct position of the cannulas via fluoroscopy or abdominal and chest x-rays. In a double cannula system, the infusion cannula must be placed in the SVC while the drainage cannula should be placed in the IVC below the diaphragmatic level; their ends at least 10 cm apart. If support is provided by a dual lumen cannula, it is important to verify that the infusion site is directed towards the tricuspid valve via Doppler echo.

**Harlequin syndrome**

Harlequin syndrome describes the situation where the upper body is hypoxemic (“blue”) whereas the lower body is fully oxygenated (“pink”). This situation occurs under peripheral femoral VA ECMO support, and it is the result of partially preserved heart function with poor lung function.

As the lung function is poor the left-side heart chambers receive non-oxygenated blood. This non-oxygenated blood is ejected as the heart function is partially preserved. The principal recipient of the non-oxygenated blood would be the coronary arteries and the brain vessels. The visceral organ would receive oxygenated blood through the femoral cannula. The level of the mixture happens at different levels, depending on how preserved is the heart function\textsuperscript{27}.

In order to detect that problem that leads to a continuous myocardial and/or cerebral perfusion with non-oxygenated blood, it is important to obtain all the arterial gases from the right upper extremity as it is the closest arterial site to the aortic root.

This situation is managed by switching the arterial cannula to axillary artery or central cannulation.
Left ventricle distention

Left ventricular (LV) distension is the result of the bronchial circulation, certain degree of aortic regurgitation and complete ECMO support. It is a significant complication that requires a prompt solution. LV distention increases myocardial wall tension leading to reduced coronary perfusion and chance of myocardial recovery. LV distension also leads to increased pulmonary capillary wedge pressure and pulmonary edema. Lastly, it may result in flow stasis and development of LV thrombus with risk of embolization/stroke.

Contemporary advances in ECMO approaches avoid this by unloading the LV. LV unloading in partially recovered heart function can be achieved by reducing the ECMO support/flow and maintaining the patient’s pulsatility. In some cases, IABP insertion increases coronary perfusion to improve contractility, and reduces the afterload, to facilitate the previous pulsatility. If these strategies are insufficient an active LV drain is needed. In case of central ECMO, a vent can be inserted in the left ventricle by opening the previous incision. In peripheral ECMO support, LV drainage can be obtained by placing a cannula in the left atrium using a transeptal approach. In case the transeptal puncture is not feasible, a small left thoracotomy may be necessary for direct insertion of the LV vent. In all circumstances, the LV vent is connected to the venous line. Other devices such as the Impella™ (Abiomed) can be used concurrently to decompress the LV.

Anticoagulation

Improvements in biocompatible materials for the ECMO circuit have reduced the difficulty in the anticoagulation of patients on ECMO support. There is no clear consensus regarding anticoagulation protocols; most centers have developed their own, usually based on
the use of unfractionated heparin infusions. In special situations, alternatives such as bivalirudin\textsuperscript{22} or argatroban\textsuperscript{23} can be used. The anticoagulant effect is monitored using ACT or PTT. In certain occasions, other measures as antifactor Xa levels or TEG may need to be used\textsuperscript{24}.

Every phase of the ECMO support requires a different anticoagulant range. Our protocol recommends – cannulation and initiation support start: 50-100 U/kg of heparin to achieve an ACT > 400 seconds; stable ECMO support: ACT between 180-200sec, PTT 60-80; weaning period, once flows are < 2.5 L/min: PTT higher than 80 sec and ACT round 300-400 are recommended. ACT or PTT should be checked every 2 hours for the first 4 days of support or until a stable therapeutic level is achieved\textsuperscript{24}. For an early detection of thrombotic complications all ECMO lines and the oxygenator should be inspected twice a day to discard the presence of clots.

**Weaning off ECMO**

Weaning ECMO support is normally a gradual process that occurs during several days. Once patient’s organs functions have recovered and stabilized, FiO\textsubscript{2} in VV ECMO and flows in VA ECMO can be gradually reduced\textsuperscript{25}.

For VV ECMO support, oxygenator settings (FiO\textsubscript{2} and flow/sweep) are reduced according to the ABG (paO\textsubscript{2} and paCO\textsubscript{2}). Once the FiO\textsubscript{2} is reduced to 40% and the flow/sweep at 1-2L, the ventilator parameters should return to non-protective settings. VV ECMO can then continue to be weaned off\textsuperscript{25}.

For VA ECMO support, the weaning process is supported by increased in arterial pulsatility, stable Swan Ganz parameters and daily assessment of heart function using echocardiography. Once the arterial pulsatility and contractility have improved, ECMO flows can be reduced after optimizing inotropic infusions and ventilator settings. The flow is reduced
to 50% of the cardiac output supported by the ECMO. If the contractility and the hemodynamic parameters remain stable for 15-30 minutes, the ECMO flows can be safely reduced another 50% until the complete wean.

In both VV and VA ECMO weaning, process longer than 4 hours should be avoided.

**CLINICAL OUTCOMES**

ECMO techniques and management carry inherently high rates of complications, some with devastating impact. Complications include those related to patient adverse events and/or adverse events related to the ECMO circuit. Patient adverse events primarily include neurological, renal, vascular, cardiac and respiratory. Circuit adverse events include problems related to oxygenator, heat exchanger, lines, pump itself (mainly thrombosis), and/or air embolization.

ECMO outcomes have been poor historically; this is especially true for adult patients undergoing ECMO. ELSO clearly recommends against ECMO consideration if the predicted mortality is <50%. Early studies for ECMO described very high mortality (>90%)\(^1\); leading to decreased interest, especially in adult patients. After technical advances, clinicians started using ECMO in highly selective otherwise healthy patient group with very high mortality probability\(^2\). These stringent selection criteria gradually were extended to other patients with less severe condition with increased expertise and improved technology.

Extracorporeal Life Support Organization (ELSO) statistics suggests almost 56% of overall survival in adult respiratory failure patients receiving ECMO, with best survival usually related to viral (65%), aspiration (63%) and bacterial pneumonia (60%) as underlying etiology for ARDS. Similarly, overall adult survival for cardiac failure patients receiving ECMO is 40%.
This difference in survival is represented in all age groups between cardiac and respiratory failure (p<0.001). Myocarditis (67%) and cardiomyopathy (49%) represents better survival compared to congenital cardiac defect (33%) 29.

Table 1 displays recent studies for VA ECMO for cardiac failure. Early (30 day) survival ranges from 24% to 65%, with survival to discharge ranges from 14% to 59%. Different complications are not mentioned in all studies but common complications include infection, bleeding incidents, acute renal insufficiency, neurological events and limb ischemia. Early studies show usually higher rates of complications. Infection rates of as high as 58% has been observed4. Highest rates for acute renal insufficiency were reported by Bakhtiary et al of almost 87%5. Neurological complication ranged from 9% to 33%. Similarly incidence of limb ischemia is noted from 7% to 36%3.

Respiratory failure supported with VV ECMO has consistently shown better outcomes compared to cardiac failure. This difference is represented at every age group including adults. Most common indication for ECMO in respiratory failure is in severe ARDS. Conducted in 1974, first clinical trial for ECMO in ARDS published its results in 1979 with 91% mortality in intervention group compared to 92% in controls1, which was very high compared to other contemporary observational studies. Studies from the early 1990s, 40% of patients survived to discharge in a small sample study published by Anderson et al28. Similarly, 54% survival was described by Kolla et al in 100 patients30 enrolled between 1990 and 1996. More recently, the CESAR trial31 examined the impact of referral to specialized center with consideration for ECMO compared to conventional mechanical ventilation with significant improvement in survival (63% vs 47%, p=0.03).
ETHICS

ECMO has inherent ethical challenges. As traditional definitions of death usually include cessation of cardiorespiratory function, the role of ECMO itself poses challenges to the ethos of end of life discussions with patient family. It is imperative that physicians provide family members with detailed knowledge of the implications on continued ECMO care versus discontinuation, in patients who are not being bridged to recovery, permanent assist device or transplant. Due to emergent nature of the procedure it may not be feasible to have these discussions beforehand, but should be initiated early in the course of the treatment to avoid potential disagreements.

Respiratory failure necessitating VV ECMO has three potential outcomes: recovery of respiratory function, patient mortality from complications of care, or irreversible multi-organ failure deeming transplant ineligibility. There is no destination device where VV ECMO may act as a bridge. Recovery is unlikely after 4 weeks of VV ECMO support, and complications increase after 14 days. Discussions should begin by two weeks, if it appears that efforts and economic resources may be futile. Unfortunately there is no universally accepted ECMO specific risk score to predict early and late outcomes. Surrogates such as the Sequential Organ Failure Assessment (SOFA) and APACHE score have been used to aid in discussions of probability with patients’ families.

While similar to above, VA ECMO is further perplexing in that VA ECMO itself provides both cardiac as well as respiratory support superior to cardiopulmonary resuscitation. Do not resuscitate (DNR) order or comfort measures are thus incompatible with this strategy.
Whereas DNR may be relevant discussion for VV ECMO, where cardiac arrhythmias can result in the need to perform CPR. ECMO used for organ retrieval, also known as Extracorporeal Interval Support for Organ Retrieval (EISOR) has its own set of ethical complications. Organ retrieval from non-heart beating donors (NHBD) can increase the donor pool, reducing the dire shortage of organs. Sole purpose of ECMO support in this situation is to improve the quality of organs harvested from the donor, after a period of life incompatible vital signs. However, the excellent resuscitation with ECMO lends to ethical debate and conflicts of interest in decision of when and whether the donor is dead.

**ECONOMICS**

Despite the heterogenous nature of ECMO, there have been some economic analyses that are enlightening. The most recent CESAR trial collaboration reviewed 180 patients in a randomized fashion to ECMO center referral versus optimal medical management for ARDS and found the cost to approximate £19,000 ($30,000US) per quality adjusted life year (QALY). Given the reference to hemodialysis as an often used benchmark, where the cost is $50,000-$70,000US/QALY and threshold to use low, ECMO may be considered cost-effective when used in selective patients with ARDS.

Cost analysis for VA ECMO is less clear. Maxwell et al analyzed almost 9000 hospital admissions using the Nationwide Inpatient Sample, between 1998 and 2009. Average daily and total hospital costs were approximately $40,000/day and $344,000 (total) respectively. When analysed, the post-cardiotomy shock cohort had most favorable outcomes and lowest resource
use/cost. From 1998 to 2009 the total annual cost of ECMO in this cohort studied increased from $109 million/year to $765 million/year. Analyses showed this was not solely driven by increased ECMO volume. Charges per patient and lengths of stays increased significantly. However, patterns showed an increased proportion of VA ECMO in non-post-cardiotomy cohorts, resulting in worse outcomes and cost-effectiveness.

CONCLUSIONS

ECMO has evolved in design, technology, patient selection, insertion techniques, adjunct devices and management in the past 45 years since it began. Outcomes have improved and indications have expanded. It remains an expeditious, cost-effective tool for rapid resuscitation of patients with cardiorespiratory failure, whose outcomes without ECMO intervention are predominately fatal. However, results are still guarded and the ethical aspects of ongoing care needs to be at the forefront of daily family discussions, in those where a bridge to transplant or definitive device are not possible.
REFERENCES


TABLE 1: Summary of recent studies with survival to discharge results after VA ECMO.

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Study period</th>
<th>Number of Patients</th>
<th>Survival to discharge</th>
<th>30-day survival</th>
</tr>
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<tbody>
<tr>
<td>Bakhtiyari</td>
<td>Cardiogenic shock</td>
<td>2003-06</td>
<td>45</td>
<td>28.9%</td>
<td>47%</td>
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<tr>
<td>Belle</td>
<td>Cardiogenic shock; Cardiac arrest</td>
<td>2006-10</td>
<td>51</td>
<td>27.4%</td>
<td>NA</td>
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<tr>
<td>Chamogeorgakis</td>
<td>Cardiogenic shock</td>
<td>2006-11</td>
<td>61</td>
<td>14.8%</td>
<td>36.1%</td>
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<tr>
<td>Formica</td>
<td>Cardiogenic shock</td>
<td>2002-09</td>
<td>42</td>
<td>38.1%</td>
<td>52.4%</td>
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<tr>
<td>Kim</td>
<td>Cardiogenic shock</td>
<td>2006-10</td>
<td>27</td>
<td>59.3%</td>
<td>63%</td>
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<tr>
<td>Lamarche</td>
<td>Cardiogenic shock</td>
<td>2000-08</td>
<td>32</td>
<td>44%</td>
<td>43.8%</td>
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<tr>
<td>Lin</td>
<td>Cardiac arrest</td>
<td>2004-06</td>
<td>55</td>
<td>29.1%</td>
<td>34.5%</td>
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<tr>
<td>Liu</td>
<td>Cardiac arrest</td>
<td>2007-10</td>
<td>10</td>
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<td>Smedira</td>
<td>Cardiogenic shock</td>
<td>1992-99</td>
<td>202</td>
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<td>Doll</td>
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<td>1997-2002</td>
<td>219</td>
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<td>Beurtheret</td>
<td>Cardiogenic shock; Cardiac arrest</td>
<td>2005-09</td>
<td>87</td>
<td>36.8%</td>
<td>NA</td>
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