

REVIEW

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) AND ADULT RESPIRATORY FAILURE

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SUMMARY : *Extracorporeal membrane oxygenation (ECMO) is a form of therapy that provides for total gas exchange when severe cardiac or pulmonary failure is unresponsive to optimal ventilatory and pharmacological management. The key component of ECMO is the transport of oxygen into blood across a semipermeable membrane. It has been successfully used to treat respiratory failure in 7400 patients with 80% to 90% survival of infants since 1975, and has become standard treatment for severe respiratory failure in newborn infants. Its use has also been successfully applied to pediatric respiratory and cardiac failure. However, some studies have not confirmed a benefit compared with the safer ventilator strategies of ARDS, as advancing technology provides venovenous access with better regulation of anticoagulation and true lung rest with 51% success rate in adult patients with respiratory failure. The outcome of ECMO for adults has shown that it is a reasonable therapy for patients with severe respiratory failure who fail to recover despite maximal conventional therapy.*

Key Words: *Extracorporeal Membrane Oxygenation, Respiratory Failure, Adult.*

INTRODUCTION

Acute respiratory failure (ARF) presents when the pulmonary system is no longer able to meet the metabolic demands of the body, and is a common cause of mortality in critically ill patients. Acute respiratory distress syndrome (ARDS) is one form of respiratory failure characterized by decreased pulmonary compliance and bilateral infiltrates (1). Unfortunately, severe respiratory failure is associated with mortality rates as high as 85% in patients in the intensive care unit (2). Survival, however, depends upon supportive management with providing adequate gas exchange while avoiding further damage to the lungs and other systems. Extracorporeal membrane oxygenation (ECMO) (now known as extracorporeal life

support) offers the possibility of reducing ventilator induced lung injury and "resting" the lungs to permit recovery of pulmonary function in the setting of ARDS (3). ECMO combined with conventional mechanical ventilation has had excellent success in treating neonatal respiratory failure, but remains a controversial treatment in adults. Herein, we review ECMO and the support for adult respiratory failure disease.

History of ECMO trials

ECMO has been successfully used to treat respiratory failure in 7400 patients with 80% to 90% survival of infants since Dr. Bartlett's pioneering efforts and the first survivor in 1975 (4). The key component of ECMO is the transport of

oxygen into blood across a semipermeable membrane. This phenomenon was first recognized in 1944 when Kolff and Berk (5) noted that blood became oxygenated as it passed through the cellophane chambers of their artificial kidney. The cardiopulmonary bypass concept was developed in the early 1950s. Devices used at that time were bubble or disk oxygenators with a direct oxygen-blood interface, resulting in marked hemolysis after a few hours of bypass, precluding their use for long-term problems (6). With the development of the first membrane oxygenator by Clowes et al. (7) in 1956, prolonged cardiopulmonary bypass (CPB) became feasible. The 1960s and 1970s were periods for advancement in techniques and also for research into prolonged pulmonary support (5, 8-11). A multi-center randomized trial was organized by the National Heart, Lung and Blood Institute (USA) to study venoarterial ECMO therapy in adults with acute pulmonary insufficiency in the 1970's (11,12). Unfortunately, survival was not improved (9.5 % in ECMO patients and 8.3 % in controls). Since then, modifications and improvements in the technique have demonstrated an increasing role for the use of ECMO in adult patients.

Major changes have occurred in the technology of ECMO and in the understanding of the approach to management of severe respiratory failure. Gattinoni et al. reported 43 % survival with venovenous ECMO in adult respiratory failure in 1988 (13). They hypothesized that first the purpose of ventilation is to excrete CO₂. Oxygenation can be achieved by inflation and airway oxygenation alone. Second, progressive lung injury in ARDS is caused in part by ventilator-induced high pressure or overdistension injury of the most normal alveoli. Third, in order to eliminate the need for high-pressure ventilation, CO₂ removal could be accomplished with venovenous access using relatively low blood flow and a large membrane lung surface area. Fourth, venovenous ECMO would allow for normal pulmonary blood flow. They used these principles in venovenous extracorporeal gas exchange with low frequency positive pressure ventilation in a variety of adult patients. Because of new technology, emphasizing venovenous access, CO₂ removal, better regulation of anticoagulation, and true lung rest, 51% success rate has been reported by several centers (3,13-18) (Table 1).

Center	Patients	Survival
Pittsburgh (3)	34	39%
Milan (13)	61	43%
Ann Arbor (14)	48	63%
Marburg (15)	40	55%
Salt Lake City (16)	40	38%
Leicester (17)	50	66%
Berlin (18)	49	55%
Total	322	51%

ECMO: Extracorporeal membrane oxygenation

V-V: Venovenous

ARDS: Acute respiratory distress syndrome

Table 1: The benefit of ECMO for ARDS: Survival from V-V ECMO.

Who should be considered for ECMO?

Patients with acute, and severe but potentially reversible ARDS (without major contraindications), primary lung allograft failure, therapy-resistant status asthmaticus, and massive pulmonary embolism are candidates for ECMO. Decompensated chronic obstructive pulmonary disease patients might possibly benefit from the application of low flow ECMO (19).

Criteria for ECMO initiation (respiratory failure in adults with 90% or greater mortality risk) (3,14).

ECMO entry criteria are established for the NIH multicenter ECMO trial (Table 2). It has been stated that approximately 1% of ARDS patients at an institution will fulfill criteria without contraindications, although this obviously depends on the characteristics of the institution. Poor gas exchange despite optimal ventilator and pharmacologic therapy [optimal therapy (1) was defined assist-or time-cycled, pressure limited ventilation, positive end-expiratory pressure (PEEP) and inspired oxygen fraction titration based on SvO₂ (mixed venous O₂ saturation), diuresis to dry weight, and maximization of the oxygen delivery / consumption ratio] in patients younger than 65 years without neurologic damage, ventilator support < 6 days, intrapulmonary right to left shunt >30%, PaO₂/FiO₂ ratio < 100 (arterial O₂ partial pressure/ inspired oxygen fraction), PaCO₂ (arterial CO₂ partial pressure)>45 despite minute ventilation > 0.2 L/kg, static compliance

Entry type	Testing time (h)	FiO ₂	PEEP (cmH ₂ O)	Qs/Qt	PaCo ₂ (mm Hg)	ICU (h)
Fast	2	1	≥ 5	-	30-45	-
Slow	12	>0.60	≥ 5	>0.3	30-45	> 48

FiO₂: Fraction of inspired oxygen

PEEP: Positive end-expiratory pressure

PaCO₂: Arterial carbon dioxide partial pressure

PaO₂: Arterial oxygen partial pressure

Qs/Qt: Right-to-left shunt fraction

ICU: Intensive care unit

ECMO: Extracorporeal membrane oxygenation

Transpulmonary shunt > 30%, total static compliance < 30 cm H₂O

Table 2 : ECMO entry criteria PaO₂<50 mm Hg, 3, 16.

<0.5 ml/cm H₂O/kg, and diffusely abnormal chest x-ray (four quadrants) are the initiation criteria for ARDS patients. Immunosuppression is not considered a contraindication for ECMO.

ECMO Exclusions

Patients with contraindication to anticoagulation (gastrointestinal bleeding, recent cerebrovascular accident, or chronic bleeding disorder), severe chronic systemic disease or another clinical condition that in itself greatly limits survival, irreversible central nervous system disease, severe chronic pulmonary disease [FEV₁(forced expiratory volume in 1 second) < 1 L, FEV₁/FVC (forced expiratory volume in 1 second / forced vital capacity) < 0.3 of predicted, chronic PaCO₂ > 45 mm Hg, chest x-ray evidence of interstitial infiltration or previous hospitalization for chronic respiratory insufficiency], total-body surface burns > 40 %, rapid fatal malignancy, chronic left ventricular failure, chronic liver failure (total bilirubin > 2 mg/dl and / or serum transaminase levels 3 times normal) or chronic renal failure (serum creatinine > 2 mg/dl or chronic dialysis therapy; relative exclusion criteria), PW (Pulmonary artery wedge pressure) > 25 mm Hg, and mechanical ventilation > 21 days are the exclusion criteria for ECMO.

ECMO Technique (3,17) (Fig. 1)

The ECMO technique for adult patients is the same as neonatal ECMO, including the venovenous and venoarterial bypass mode with lung rest. Venovenous extracorporeal membrane oxygenation (V-V ECMO) is a procedure to both oxygenate and remove CO₂ by pumping patient's venous blood through a membrane lung and then

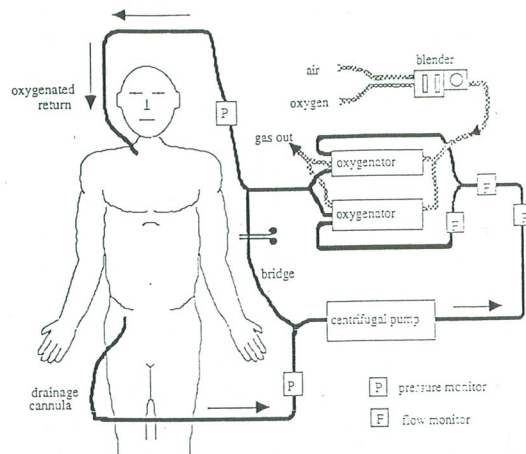


Fig - 1 : ECMO circuit (3, 17). Cannulation above is for V-V ECMO; circuit setup the same for V-A of ECMO.

returning it to the venous system. Venoarterial (V-A) ECMO utilizes the same circuit but returns blood into the patient's arterial system which allows the circuit's centrifugal pump to provide a cardiac output of 4~5 L/min in the event of major cardiac failure.

The protocol for ECMO at the University of Pittsburgh (3) includes the use of a Medtronic Carmeda heparin-bonded system (Medtronic Cardiopulmonary, Anaheim, CA). Initial oxygenation is provided by two parallel Medtronic Maxima hollow fiber oxygenators. A Biomedicus BP-80 centrifugal pump and flow probe (Medtronic Biomedicus, Eden Prairie, MN) are used, along with heparin bonded tubing. Heparin is administered to maintain an activated clotting time (ACT) of 180 to 200 sec (Hemochron celite,

International Technidyne Corporation, Edison, NJ). Heparin administration is delayed 10-12 h in patients who are considered to be at increased risk for bleeding postoperatively. Oxygenators are changed if foaming occurred. Maxima oxygenators are replaced with Avecor silicone rubber membrane systems (Model 3500, Avecor Cardiovascular Inc., Plymouth, MN) when it becomes necessary to change oxygenators. Initial priming is with Plasmalyte A (Baxter Healthcare Deerfield, IL). This is displaced with 3 units of cell saver washed bank blood, 75 meq sodium bicarbonate, and 500 mg of calcium chloride. The total priming volume is 1,800-2,200 ml. The choice of VV or VA support is based on the patient's hemodynamic stability and the surgeon's discretion. VA cannulation is either by right atrial to aortic (sternum left open) or common femoral vein to common femoral artery. When femoral artery cannulation is performed, great care is taken to assure that the cannula tip is located high in the abdominal aorta. In addition, right radial artery oxygen saturation is routinely monitored and maintained above 90% to assure adequate central oxygenation. Femoral artery cannulation is routinely accompanied by insertion of a small cannula distal to the cannulation site to ensure adequate lower extremity perfusion. Carotid artery cannulation is not performed; axillary arterial cannulation can be also performed. VV cannulation typically is by common femoral vein to common jugular vein. Cannulation is performed by percutaneous techniques when possible. For patients whose cannulation is changed from VA to VV or from VV to VA, classification is based on the type of cannulation during the majority of the time on ECMO support.

Hematocrit is maintained at >30% for VA support and >35% for VV support. Platelet count is maintained at greater than 100,000/mm³ if the patient is bleeding. Ventilator settings are reduced during ECMO, typically with FiO₂ at 30-40%, respiratory rate 4 breaths/min, and peak airway pressure of 25-30 cm H₂O above 10cm H₂O positive end-expirating pressure. For lung transplant patients, immunosuppression is continued throughout the course. Patients are weaned from ECMO when normal hemodynamics and gas exchanges are demonstrated with decreased inotropic support and mechanical ventilation. Markers of lung recovery are: a)

improvement in chest radiograph and lung compliance, b) ability to clear CO₂ with decreasing gas flow through oxygenators, c) ability to maintain PaO₂ with decreasing blood flow through circuit, d) oxygenation improvement is measured on 5 PEEP and 40% FiO₂.

Venoarterial (V-A) ECMO

The major indication is cardio-respiratory failure. The cannulation of venous drainage is from inferior caval vein (IVC) via femoral vein (~28F) and/or additional Internal jugular vein (IJV) drain in case of the inadequate venous drainage. The oxygenated return is from aortic arch via femoral artery (~22F).

Non-pulsatile systemic perfusion and excellent CO₂ removal are the features of V-A ECMO. Arterial saturation is sensitive to changes in native cardiac output. The differentiations of V-A ECMO from full cardiopulmonary bypass are defined in Table 3. Erroneous cardiac output determinations are falsely high because a smaller temperature change is detected due to steal of injection into ECMO cannula [with both V-A and V-V ECMO the cardiac output should be determined by injection into a right ventricular (RV) port of the pulmonary artery (PA) line]. Ischemia distal to femoral artery cannulation (distal femoral artery flow often augmented with a small cannula connected to the ECMO circuit), systemic emboli, potential ischemic insult to lung (animal data suggests significant injury within 6 h of total CPB and diffuse alveolar damage) and thrombi in alveolar capillaries within 18 h are the possible combinations. Lung allograft in transplant patients may be more prone to ischemic injury due to absence of bronchial blood supply, and non uniform arterial blood gases are the ongoing

	V-A ECMO	CBP
Pulmonary flow and native CO	Conserved	Lost
Duration of procedure	Days to weeks	Hours
Anticoagulation	Partial	Full
Bubble traps and Blood filters	No	Yes
Thoracotomy	No	yes

V-A ECMO: Venoarterial extracorporeal membrane oxygenation

CPB: Cardiopulmonary bypass

CO: cardiac output

Table 3 : Differs between V-A ECMO and full CPB.

problems with V-A ECMO.

Venovenous ECMO

The indication is major respiratory failure with preserved cardiac function. High flow venovenous ECMO is characterized by circuit flows of 4-5 L/min with goal of meeting demands of both oxygenation and CO₂ removal.

The cannulation of venous drainage is from IVC via femoral vein (~28F), and the oxygenated return is from superior vein cava (SVC) via right IJV (~22F).

V-V ECMO provides oxygenation of mixed venous blood, excellent CO₂ removal, and full pulmonary blood flow maintained. Arterial saturation sensitive to changes in cardiac output, pulmonary shunt and ECMO flow. Problems with V-V ECMO are erroneous cardiac output determinations (as with V-A), lower risk of arterial embolization (unless paradoxical), lower risk of bleeding than venoarterial ECMO, and variability to use SVO₂ as a measure of cardiac reserve and to titrate support; SVO₂ decrease as CO increase.

The goals are during V-V ECMO are to keep venous O₂ saturation > 0.85, arterial O₂ saturation > 0.80 - 0.90 (typically ~ 90%), PaCO₂ maintained ~ 35-45 mm Hg, hematocrit (Hct) maintained >35% (40-45% in almost all programs), and sedation + paralysis initially (when stable on ECMO, allow to awaken).

Ventilator management with ECMO (V-A and V-V) -> Aid in oxygenation

Lowest FiO₂ to maintain PaO₂ sat > 90%, PEEP of 10-15 cm H₂O initially, maintenance of functional residual capacity (rate 4-10/min, and tidal volumes set by limiting peak airway pressures to 35 - 40 cm H₂O), and CO₂ removal regulated by ECMO "sweep gas flow" (usually 1-4 L/min) are the ventilator management goals in ECMO.

Anticoagulation during ECMO (V-A and V-V)

Heparin is used to keep ACT 180 -200 unless bleeding occurs (normal ACT values 90 to 130 seconds). If PT >15 sec, Fresh Frozen Plasma (FFP) is transfused as a source of antithrombin III (AT III levels remain ~ 80% of normal for first 3-4 days then decrease to 60%. Low ATIII makes patient difficult to heparinize). Bleeding, empirically for

platelet counts < 80,000 in immediate post surgical patients, and empirically for platelet counts < 30,000 in medical patients are the indications for platelet transfusion. On the other hand, platelets fall over first 5-7 days the stabilize typically in 50-100,000 range; platelet counts often increase only minimally with transfusion.

The advantages of heparin bonded Carmeda system

Heparin covalently bonded to all surfaces of circuit including cannulas except for biohead (the part of the centrifugal pump in contact with the blood). It decreased thrombogenicity, diminished activation of platelets, complement, and coagulation. Heparin is still used since thrombosis in occurs areas of stasis. It provides shortened life of oxygenators due to increased brittleness of hollow fibers and varied pore size resulting in plasma leakage.

What is the role of the perfusionist?

The perfusionist is responsible for the set up, troubleshooting and 24-hour monitoring of ECMO system. He/she maintains circuit flow without excessive circuit pressures, suggests volume infusion as needed to maintain extracorporeal flow, maintains 100% O₂ saturation in outflow catheter, adjusts sweep gas (1-4 L/min) to clear CO₂, and monitors arterial blood gases (arterial, pre- and post- oxygenator) and ACT.

DISCUSSION

ECMO results have improved since 1970's. In part, this may be due to better case selection, venovenous perfusion, and improvement in the technology of long-term perfusion. It may also be due to the fact that the conventional management of today has improved survival in respiratory failure, anyway (20,21). But the question is whether ECMO is superior to conventional treatment or not. Recently, a collaborative ECMO trial showed conclusively that in the neonatal population, the morbidity and mortality of severe respiratory failure are reduced when ECMO is used instead of conventional treatment (22). On the other hand, the occurrence of pulmonary hypertension and persistent fetal circulation in this age group is dissimilar to the adult- population, but the problem of ventilator lung injury from barotrauma/volutrauma and oxygen toxicity is the same in all patients. The potential complications of ECMO are

similar in neonates and adults, but fortunately ECMO can be conducted safely by properly trained personnel without specific ECMO-related morbidity. It has been emphasized that the long-term functional status of ECMO survivors is good, and most patients return to their former occupations (23,24). Of course, detailed follow-up study should be done to assess the long-term physiologic and psychological outcome in ECMO patients.

Lung recovery appears to be correlated with time spent undergoing mechanical ventilation before ECMO. The most severe lung injury is seen in patients with elevated pulmonary artery pressures (75% of systemic pressures or greater), decreased aeration and lung compliance, and diminution of transpulmonary gas exchange. Irreversible lung injury is presumably due to capillary microthrombosis and obliteration, replacement of alveolar architecture with fibrosis, and an accompanying inflammatory cellular infiltrate (25). Whether less time on the ventilator before ECMO selects the more treatable conditions or a longer time on the ventilator contributes to parenchymal injury attributable to high ventilator pressures and high oxygen concentration is not known.

Even if we will be in the learning curve, a randomized study should be done in centers in Turkey, with standardized technology, and in a well-characterized patient population with proven physiologic markers of mortality risk. A phase I adult ECMO study should be done in patients with ARF, ventilated less than 5 days, in centers with at least 50 cases when heparin bonded circuits are routinely available.

Recently IVOX (intravascular oxygenator) has been used in some intensive care units. (26). The device does not need blood pump like ECMO and performs intracorporeal gas exchanges via a small elongated hollow fiber membrane oxygenator designed to lie within the caval vein. The amount of gas change in IVOX is less than ECMO, however, the equipment is simple and there is no effect to hemodynamics and body temperature. Perhaps, its cost is less expensive, but it has not been used very commonly because the gas transfer rate by means of the IVOX device constitutes 1/4 to 1/3 of the total metabolic requirement of ARDS patients.

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