REVIEW ARTICLE

Veno-Arterial Extracorporeal Membrane Oxygenation in the Adult: A Bridge to the State of the Art

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Abstract: Despite the technological advancements in the last 40 years, conditions such as refractory cardiogenic shock and cardiac arrest still present a very high mortality rate in real-world clinical practice.

In this light, we have reviewed the techniques, indications, contraindications, and results of the so-called Veno-Arterial Extracorporeal Circulatory Membrane Oxygenation (VA-ECMO) in the adult population to evaluate the current results of this temporary cardio-pulmonary support as salvage and/or bridge therapy in the patient suffering from refractory cardiogenic shock or cardio-circulatory arrest.

The results are encouraging, especially in the setting of refractory cardiogenic shock and in-hospital cardiac arrest. Among a selected population, the prompt institution of a VA-ECMO may radically change the prognosis by sustaining vital functions while looking for the leading cause or waiting for the reversal of the temporary cardio-respiratory negative condition.

The future directions aim to standardized and shared protocols, miniaturization of the machines, and possibly the institution of specialized "ECMO teams" for in and the out-of-hospital institution of the tool.

1. INTRODUCTION

The opening of the Pandora's box containing all the evils of the world - as stated by the ancient Greeks - must have especially attacked the heart of the human beings if it is true that cardiovascular diseases are still the most relevant cause of death worldwide [1, 2].

Conditions like refractory cardiogenic shock by every cause and cardio-circulatory arrest still present a very high mortality rate. Despite the scientific and technological achievements of the last 40 years, these conditions still represent a challenge for the medical community [3].

For example, if we look at the cardiogenic shock as a complication, the myocardial infarction, despite the introduction of primary angioplasty and the improvements in intensive care management have dramatically reduced the rate of in-hospital deaths in the last ten years, this downward curve in mortality has drastically decelerated.

Currently, one in two patients hospitalized for cardiogenic shock dies during the hospitalization [4].

More detrimental are the data regarding the prognosis of cardiac arrest. Many published series report a survival rate after 30 minutes of Cardio-Pulmonary Resuscitation (CPR) between 7% and 18% [5].

The aim of this paper was to review the techniques, indications, contraindications, and the results in the adult population of the temporary cardiopulmonary assist devices, collectively named as Extracorporeal Membrane Oxygenation (ECMO) or Extracorporeal Life Support (ECLS) [6].

1.1. The Principle

The principle of the Veno-Arterial (VA) ECMO is a short-term (generally hours to few days) cardio-pulmonary assistance in many cases of acute cardio-respiratory failure. The system employs the common principles of Cardio-Pulmonary Bypass (CPB), in an intensive care setting [7].

Currently, two types of assistance are available: one requiring the support of both cardiac and pulmonary functions, the so-called Veno-Arterial ECMO (V-ECMO), and one only replacing the respiratory function, named Veno-Venous ECMO (VV-ECMO) [8, 9].

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1.2. The Setting

An ECMO consists of a transportable cardio-pulmonary machine (Fig. **1**) that provides an adequate flow and a venous and arterial cannula to be connected to the patient.

Fig. (1). A transportable ECMO machine. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

There are two ways to implant the cannulae (required to remove the deoxygenated blood and reinfuse the oxygenated one): central and peripheral (Fig. **2**).
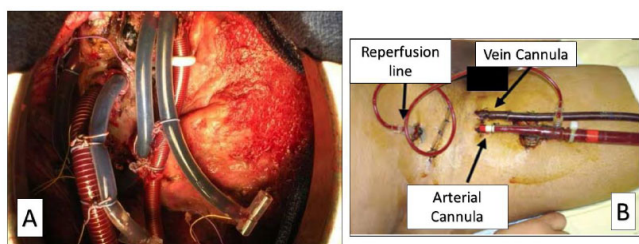

Fig. (2). An example of central (A) and peripheral (B) ECMO implantation. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The first way is surgical, and the correct environment for the implantation is the operating room; the venous drainage is achieved *via* the right atrium while the arterial line is connected to the ascending aorta [10].

The peripheral way of cannulation classically uses the common femoral vein for the inflow and either the common femoral artery or axillary artery for the outflow [11].

The peripheral cannulation can be accomplished with either a surgical or percutaneous approach using the classical *Seldinger technique* (Fig. **3**).
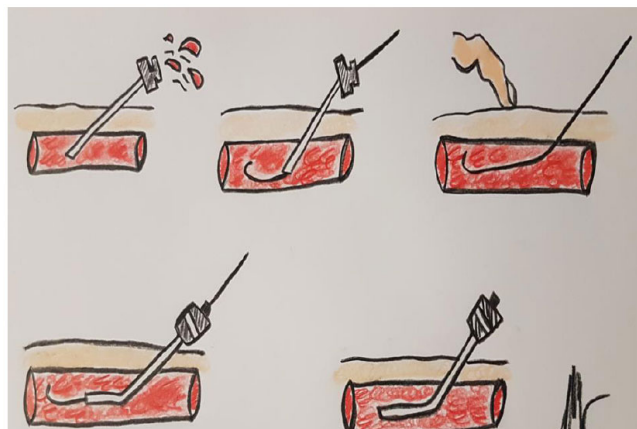

Fig. (3). Seldinger technique for percutaneous vascular access. After the needle puncture of the vessel, an adequate guidewire is inserted within the vasculature. The needle is then removed, maintaining the access, and an appropriate sheath or cannula is inserted over-the-wire (for the large-bore cannulae, the use of progressively larger dilators is advisable to reduce the risk of vascular damage). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In case of femoro-femoral cannulation crucial to provide a distal perfusion to the inferior limb by a means of a small cannula or sheath connected to the arterial line.

Currently, mini-ECMO devices with heparin-coated cannulas are available [12] to facilitate transportation and to reduce the thrombo-embolic complications of the system.

2. THE GOAL OF THE TOOL

The ECMO has no definitive therapeutic purpose but is purely designed for short-term support of vital functions in emergency acute cardio-respiratory failure [13].

This kind of "bridging" has three main outcomes:

- Support the vital functions until the recovery of the myocardial function sharply depressed ("*bridge to recovery*") [14].
- Support the vital functions while waiting for cardiac transplantation ("*bridge to transplant*") or curative interventional therapy or surgery ("*bridge to destination therapy*") [15, 16].
- Support the vital function while waiting for a diagnosis and the proper therapeutic decision-making ("***bridge to decision***") [17].

Despite the enormous technical and scientific progress and improvement in the management of these acutely depressed patients, a disproportionate number of these die during hospitalization [18].

The Extracorporeal Life Support Organization (ELSO), the international organism that records and analyses the ECMO procedures since 1989, provides two main classes of indications: cardiovascular (Veno-Arterial configuration) and respiratory (Veno-Venous configuration) [19].

Generally, ECMO is indicated when conventional therapies fail to overcome the clinical problem; we can, therefore, collectively call them *refractory conditions*.

3. PRINCIPAL INDICATIONS FOR THE INSTITUTION OF VA-ECMO

Current cardiovascular indications for VA-ECMO implantations in the adult are listed in Table **1**.

The most frequent remains refractory cardiogenic shock, defined as a persistent hypotensive state (systolic blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg) in normal preload conditions that do not respond to a full dose of inotropes and vasoconstrictors and intra-aortic balloon counter-pulsation (IABP), if appropriate, and that is accompanying by oligo-anuric state (hourly diuresis less than 20 cc or 0.5 cc/kg) [20].

Table 1. Main cardiovascular indications for the implantation of veno-arterial ecmo in the adult.

Refractory Cardiogenic Shock
Refractory cardiac arrest
Acute myocarditis
Primary cardiac graft failure
Septic shock
Hypothermia
Cardiac drugs poisoning
Pulmonary embolism
Peripartum cardiomyopathy
Refractory anaphylactic shock
Trauma to myocardium
Massive hemoptysis or pulmonary hemorrhage
Pre- or postprocedural circulatory support for high-risk interventional procedure
Preoperative stabilization after myocardial infarction presented with ventricular septal defects

The second frequent indication is refractory cardiac arrest, normally defined as an absent return to a spontaneous rhythm after 30 minutes of effective CPR [21].

Another recent indication is the hemodynamic stabilization in patients suffering from post-myocardial infarction ventricular septal defects.

4. CONTRAINDICATIONS TO ECMO

There are also formal contraindications to the temporary mechanical support, either absolute or relative.

Absolute contraindications are unrecoverable heart and patients not eligible for a transplant or Ventricular Assist Device (VAD), advanced age (> 85 years), chronic organ dysfunction (severe emphysema, cirrhosis, severe renal failure), poor compliance, and preexisting functional status (financial, cognitive, psychiatric, or social limitations), prolonged CPR (> 60 minutes) without adequate tissue perfusion or un-

witnessed cardiac arrest, recent (within three months) cerebral hemorrhage, aortic dissection, severe aortic regurgitation.

Relative contraindication (and other considerations to be faced during the decision-making process) are contraindication to anticoagulation, morbid obesity, advanced age, renal or liver failure, active malignancy, known significant peripheral vascular disease, heparin-induced thrombocytopenia (HIT) [22].

5. WEANING FROM ECMO

Generally, it is recommended to maintain the assistance for at least 48-72 hours, independently from the underlying etiology. However, an instrumental and clinical evaluation is normally made every 12 hours.

The weaning process is dynamic, with several adaptations from different Centers, and considers many clinical and instrumental features. An example is reported in Table **2**.

Table 2. Example of a weaning process from ecmo.

Expect Early Signs of Recovery within One Week of Support
The pulsatile curve on invasive pressure monitoring > 24 hours
Optimize inotropes and constrictors and reduce flow to 50%, then 25% if stable hemodynamics
Progressive decreasing or stability of lactates
Left ventricular ejection fraction > 15-20%
Clamp circuit and allow recirculation for a trial period of 30 minutes to 4 hours
Flush cannulae with heparinized saline continuously or flash from the circuit every 10 minutes to avoid cannula thrombosis

The process begins once it is ongoing, the recovery, as demonstrated by a pulsatile arterial curve for at least 24 hours and echocardiographic signs of systolic functional recovery [23].

Usually there is a progressive reduction in the flow provided by the machine. An example of this decrease could be: ten to fifteen minutes at 75% of the theoretical flow. The same amount of time at 50% and 25% and at the end fifteen minutes at an output of 1 liter/minute while optimizing inotropes.

If hemodynamically stable, the circuit may be clamped for 30 minutes to 4 hours while flushing the cannulae to avoid local thrombosis [24].

6. COMMON COMPLICATIONS DURING ECMO

Although the ECLS provides an excellent opportunity for the patients' salvage, it is burdened by numerous and clinically relevant complications (Table **3**).

Keeping in mind those numerous complications is fundamental in the decision-making process and especially in the day-by-day-management of the ECMO patient [25].

7. STATE OF THE ART

The extracorporeal life support (ECLS) is an effective technique of temporary respiratory and/or circulatory support in patients with acute severe respiratory failure, cardiogenic shock, or cardiac arrest that are refractory to conventional interventions [26, 27].

This tool has no therapeutic purpose but is purely designed to support vital functions in the emergency scenario of abrupt cardio-respiratory failure [28].

Cardiogenic shock and cardiac arrest refractory to conventional therapies still have a very high mortality rate. In more than 75% of cases, cardiogenic shock is related to acute myocardial infarction (MI), and it possesses a mortality rate that - according to various published series - is still between 40 and 60% [29].

Table 3. Common complications during ECMO.

Bleeding Complications (20-60%) **Site of Cannulation Hemorrhage** **Hemothorax, Hemomediastinum** **Cerebral, Digestive, Tracheobronchial,** *etc*
Thrombo-embolic and Ischemic Complications (6-20%) Arterial (ischemic limb, amputation) Venous
Cerebral Complications (3-18%) Transient ischemic attack / ischemic stroke Hemorragic stroke
Infectious Complications (5-25%)
Renal Complications (10-60%)
Miscellanea Arrhythmias Hemolysis Ipothermia Ventricular distension Thrombosis of the circuit Pulmonary oedema Multi-organ failure (MOF) Heparin-induced thrombocytopenia (HIT)

Furthermore, this high mortality burden has remained unchanged despite the early availability of interventional cardiology procedures and IABP implantation.

Cardiogenic shock is also a rare complication (1%) of open-heart surgery, but with a mortality rate even higher (75%) [30, 31].

To avoid unnecessary or futile use of ECMO, which might consume resources and expose patients to possible ECMO complications, many considerations must be pursued to identify the appropriate candidates for ECMO support.

The hardest point for the physicians is to do so in the shortest amount of time.

Advanced age, female sex, morbid obesity, diabetes, renal insufficiency, pre-ECMO blood lactate level, elevated CK-MB levels, low serum albumin level, low platelet count, poor cardiac systolic function and logistic EuroSCORE more than 20% are independently associated with in-hospital death in patients undergoing ECMO after cardiac-related procedures [32].

In recent years different risk scores have been evaluated for ECMO purposes.

The REMEMBER (pRedicting mortality in patients undergoing veno-arterial Extracorporeal MEMBrane oxygenation after coronary artEry bypass gRafting) score incorporates six simple pre-ECMO variables and demonstrated good performance (AUROC 0.85) in the derivation cohort. All these parameters are readily measurable and available to clinicians before VA-ECMO implantation. Older age is important in determining in-hospital death, which was reflected in its weighting in the REMEMBER score. The other five variables had similar weightings in the score. These findings also confirmed that the presence of left main disease, elevated CK-MB >130 IU/L, acute kidney injury, and thrombocytopenia at ECMO initiation were associated with poorer outcomes. In addition, an inotropic score >75 was related to short-term death, which was used to roughly estimate the severity of the pre-ECMO status [33].

The score might also aid in family counseling and shared decision-making relative to clinical outcomes and help clinicians identify high-risk post-CABG patients who may suffer poor outcomes despite the use of the VA-ECMO.

In the past few years, the SAVE [34] and ENCOURAGE scores [35] have been developed to predict the survival of patients receiving ECMO for refractory cardiogenic shock. Schmidt *et al*. also developed the "Survival After Veno-arterial ECMO (SAVE)" score to predict survival after VA-ECMO for refractory cardiogenic shock using 12 pre-ECMO parameters: age, weight, diagnosis, chronic renal failure, acute pre-ECMO organ failure, peak inspiratory pressure, duration of intubation, preECMO cardiac arrest, pulse pressure before ECMO, diastolic pressure before ECMO, HCO_3 level before ECMO and a constant value to add to all calculations of SAVE score.

Chen *et al*. created a strong predictive survival model specifically for patients receiving VA-ECMO using the combination of blood lactate level and SAVE score, which they called the modified SAVE score. This score resulted in better discrimination in the mortality prediction model.

This study showed that increased lactate levels gradually increased the hazard ratio; the mortality risk increased by 1% with every increase of 1 mg/dL.

Lactate levels discriminated survivors from non-survivors with an AUC of 0.79. When lactate was combined with the SAVE score, the mortality prediction achieved the highest AUC of 0.84.

The EuroSCORE [36] and SOFA [37] scores are widely used in the fields of cardiac surgery and critical care, respectively, but to date failed to be fully adaptable to ECMO risk stratification.

Combes *et al*. evaluated the outcomes and the quality of life in the medium to long term follow-up in refractory cardiogenic shock patients undergoing ECMO [38].

This work examines 81 refractory cardiogenic shock patients; 55 having the medical indication to ECMO, 16 with the post-cardiotomy syndrome, and 10 with primary cardiac transplant failure. The 30-day survival was 42% of the population (34 patients in total). Independent predictors of mortality in the intensive care stay were the positioning of ECMO under external cardiac massage and the oligo-anuria after ECMO institution. In this series, a strong predictor of success was the diagnosis of myocarditis ("bridge to recovery").

The assessment of the quality of life was done by following-up 28 patients on an average period of 11 months; the data showed a general score lower than healthy controls but higher compared to other categories of patients, such as those on chronic dialysis or recovered from Acute Respiratory Distress Syndrome of the adult (ARDS).

Regarding the post-cardiotomy syndrome, several works show higher percentages of in-hospital death, possibly driven by inadequate myocardial management and protection during the cardioplegic arrest. Doll *et al*. analyzed this subgroup of cardiogenic shock bridged by ECMO and reported, despite an elevated percentage of complications, a 30-days survival rate of 53% [39, 40].

Refractory cardiac arrest has a much more detrimental prognosis compared to cardiogenic shock, with only 10% of patients that survive after 30 minutes of advanced cardiac life support [38].

In recent years the international literature has been populated by encouraging data on the use of ECMO as a temporary life-saving tool in this context [39].

An interesting aspect relates to the use of ECMO in case of witnessed in-hospital cardiac arrest. The literature generally reports a poor prognosis of this condition, with a survival rate between 7 and 18% [41, 42].

When ECMO is applied in selected patients with reversible cardiacarrestcauses, retrospective series have reported survival rates of between 28 and 42%; 40% in a large meta-analysis [43].

Bednarczyk *et al*. published an interesting monocentric retrospective analysis [44]. The study analyzed 32 consecutive patients with witnessed in-hospital cardiac arrest undergoing immediate resuscitation. The average length of cardiac arrest was 25 ± 23 minutes; the average duration of the mechanical support 70 ± 46 hours. The mortality rate under ECMO involved 7 patients (21.9%), the same number wasthe candidate for another form of long-term care, while 18 (56.3%) were successfully weaned. The average length of stay in intensive care was a week. 47% of survivors reported no neurological sequelae to at 30 days.

Out-of-hospital cardiac arrest is still the Achille's heel of the ECMO, presenting with the absolute worst prognosis. The main factor related to the poorest outcome of this subgroup of the patient is the long delay between the onset of the cardiac arrest and the effective ECMO implantation.

Johnson *et al*. collected data on 26 consecutive outpatients' cardiac arrest [45]. The rhythm of the presentation was ventricular fibrillation or pulseless ventricular tachycardia. The average time between the cardiac arrest and the implantation of ECMO was 77 ± 55 minutes; 23 patients were implanted within one hour from the beginning of CPR and as many as 20 were implanted under chest massage. The survival rate was low, with only 4 patients (15%) weaned.

A fundamental limitation of all the published data on the ECMO field is the lack of large controlled randomized trials. This is mostly related to the critical clinical situation to be treated and the non-uniformity of clinical and laboratory definition of refractory shock or cardiac arrest.

An attempt to summarize and critically analyze the results of the increasingly growing published series on the subject comes from a meta-analysis of Xie *et al* [46]. The subject was the results of Veno-Arterial ECMO for refractory cardiogenic shock, cardiac arrest and myocarditis. Observational studies and small clinical trials with a minimum of 10 patients enrolled since 2000 were the criteria for searching the references.

A total of 2355 references were identified within 7 databases (including PubMed, MEDLINE, and Cochrane). A total of 1199 patients in 22 studies were analyzed. The metanalysis reported overall survival at discharge was 52, 8%. Half of the patients refractory to conventional therapies that would probably die have finally been weaned.

If we look at the survival rate according to the leading indications, we observe that the most favorable prognosis is for the myocarditis group (66, 7%), followed by refractory cardiogenic shock (42, 1%) and the cardiac arrest (35,9%). The most commonly reported complications were neurological (13.3%), infective (25.1%), and kidney impairment (47%).

CONCLUSION

Despite the enormous scientific and technological progress of the last 40 years, conditions like refractory cardiogenic shock and cardiac arrest are still burdened with an unacceptable high hospital mortality rate.

ECMO is a relatively new possibility of short-term life support-that is rapidly evolving, driven by the improvements of the technological aspect by a deeper knowledge of the field.

In the recent 10 years, there has been a sharp increase in the use of this technique. Although ECMO is the only chance for many critical situations, it should be noted that it is also burdened by numerous complications.

Furthermore, due to the high cost in terms of material and human resources, it is recommended a careful case-by-case evaluation of the indication.

Currently, the peripheral, totally percutaneous approach is the most employed by virtue of its intrinsic rapidity of implantation and efficacy.

Acute myocarditis from any cause and some subsets of refractory cardiogenic shock present the best prognosis,

while the road to more favorable outcomes in the cardiac arrest setting is still sharp, even though many improvements have been reported, especially in the cases of in-hospital events.

Available data are only extracted from small observational studies, related meta-analysis and a few little clinical trials; it is desirable to establish rigidly uniforms criteria regarding the definition of shock and other clinical variables of interest to standardize the results and minimize inter-centers bias.

The future directions of this fascinating field could be wider availability of the tools necessary to institute the EC-MO, even on the ground, the formation of more and more specialized "ECMO teams", and technical and pharmacological improvements to reduce the complications and ameliorate the final destination therapies.

We are not able to close the Pandora's box, but we must fight against its evils.

CONSENT FOR PUBLICATION

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