Chapter

Extracorporeal Membrane Oxygenation as a Bridge to Cardiac Transplantation

Nandini Nair and Enrique Gongora

Abstract

Extracorporeal membrane oxygenation (ECMO) is a technique used for temporary support of patients with end-stage heart or lung failure. This review will focus on the venoarterial ECMO system and its use as a bridge to other long-term durable devices and/or cardiac transplantation. It can be used as a bridge to decision because it helps to gain time to stabilize the patient for further evaluation for long-term treatment such as durable mechanical circulatory pumps or transplantation. ECMO is evolving as a treatment for patients waiting on the transplant list. Increasing utilization of ECMO in adults has revealed some of the common complications such as bleeding and coagulopathy which impact survival in this patient population. The use of VA ECMO as a technique for rescuing patients from cardiogenic shock is very attractive. However, considering the extensive set of complications and the mortality it brings with it makes it a less attractive option as a direct bridge to cardiac transplant. The literature currently on this subject is very scanty and limited to a few studies of small numbers of patients. Further definitive research is needed for consensus on the role of VA ECMO as a bridge to cardiac transplant.

Keywords: ECMO, bridge to transplantation, extracorporeal life support

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a technique used for temporary support of patients with end-stage heart or lung failure. It can be used as a bridge to decision because it helps to gain time to stabilize the patient for further evaluation for long-term treatment such as durable mechanical circulatory pumps or transplantation. The use of ECMO as a direct bridge to cardiac transplantation may unmask the complications in these critically ill patients leading to unfavorable posttransplant outcomes in some instances; however, it is now becoming the mainstay of treatments for patients waiting on the transplant list. The history of ECMO starts with the advent of the heart-lung machine invented by Gibbon [1, 2]. Further modifications leading to devices that are sustainable for longer periods of time gave rise to the technique of ECMO used today [3–5].

The use of ECMO in humans was first initiated in the pediatric population [3, 4]. Adult ECMO gained importance and is being used increasingly since the first randomized clinical trial by Peek et al. which showed a positive outcome in adults with respiratory failure [6]. This has been followed by many reports of success in H1N1

influenza patients [7]. Anselmi et al. recently reported the use of ECMO in pregnant patients [8]. Increasing utilization of ECMO in adults has revealed some of the common complications such as bleeding and coagulopathy which impact survival in this patient population. The delicate balance between adequate anticoagulation and bleeding complications presents one of the greatest challenges of ECMO therapy today.

The ELSO (Extracorporeal Life Support Organization) was established in 1989. The ELSO was formed as an offshoot of a study group that began in 1984 discussing cases. The ELSO focuses on collection and sharing of data and has fostered a rich collaboration among the majority of centers performing ECMO. The ELSO has hence remained a good resource for surgeons, neonatologists, nurses, perfusionists, respiratory therapists, biomedical engineers, critical care physicians, and heart failure cardiologists.

A total of 73,000 ECMO procedures were recorded by the ELSO as of early 2016 of which greater than 25% were performed in adult patients [9]. From 2006 to 2011, adult ECMO volumes increased greater than four times in the United States [10]. Adult ECMO has increased in volume due to its usefulness in improving survival in ARDS (acute respiratory distress syndrome) patients [11]. Additionally, with the improvement in technology, highly specialized hospitals have evolved the capabilities to transport critically ill patients from rural areas to their critical care units making it possible for rural populations to be able to receive advanced care [12, 13].

This review will focus on the venoarterial ECMO system and its use as a bridge to other long-term durable devices and/or cardiac transplantation.

2. The ECMO circuit

The ECMO circuit (**Figure 1**) in its most basic form consists of a pump that is capable of pumping blood it receives from the drainage cannula to the membrane oxygenator which then leads to a heat exchanger. The oxygenated temperature-optimized blood is then returned to the patient by the return cannula. ECMO cannulation can be done centrally through the right atrium and ascending aorta or peripherally via the femoral artery and vein. The type of cannulation used whether central or peripheral influences the outcomes as the complications differ. When central cannulation is used, bleeding requiring transfusions is higher. In central cannulation higher rates of reoperation are also noted. Increased complications will decrease survival and increase resource utilization. On the other hand, peripheral cannulation has been noted to produce fewer bleeding complications. It can be

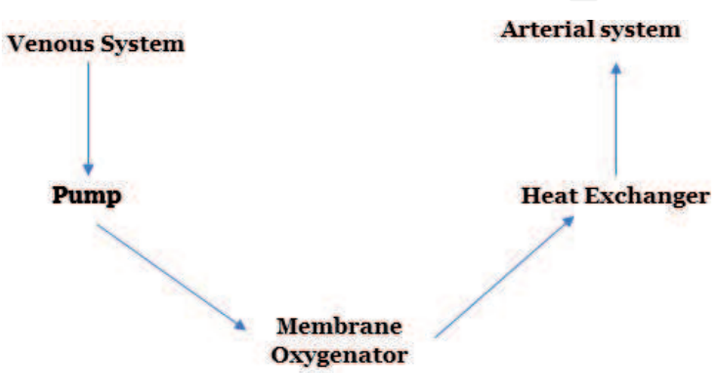

Figure 1.
VA-ECMO circuit.

placed in a shorter time and at the bedside. However, the complication of limb ischemia occurs equally in both types of cannulations.

ECMO circuits are set up depending on the organs that need to be bypassed. When both heart and lungs have to be bypassed, the venoarterial ECMO (VA-ECMO) is used as shown in (**Figure 1**). The VA-ECMO circuit provides both gas exchange and hemodynamic support as blood is pumped from the venous to the arterial systems. On the other hand, if only the lungs need to be bypassed, the veno-venous circuit (VV-ECMO) facilitates only gas exchange with no hemodynamic support. In VV-ECMO blood is removed taken out of the venous system and oxygenated and pumped back into it.

VA-ECMO is designed to provide cardiac and pulmonary support. Deoxygenated blood is drained from the venous system, and oxygenated blood is returned into the arterial circulation, in a similar fashion to standard cardiopulmonary bypass. In the VA-ECMO system, central cannulation is achieved by draining blood directly from the right atrium and returning oxygenated blood to the proximal ascending aorta. Peripheral cannulation uses blood drained from the proximal femoral vein/jugular vein which is oxygenated and then returned to the carotid/axillary/femoral artery. The Seldinger technique is used typically to achieve the cannulations.

Two types of pumps are currently available for use in ECMO circuits. They are centrifugal pumps and roller pumps. Centrifugal pumps are smaller and pump blood by providing a pressure differential across a pump head that contains a magnetically driven impeller revolving at speeds up to 3000 revolutions per min. On the other hand, roller pumps push blood across the circuit by progressively compressing segments of tubing along a curved pathway. Centrifugal pumps have been associated with a lesser degree of hemolysis compared with roller pumps and decreased requirement of anticoagulation. Therefore, centrifugal pumps are being increasingly used in in adult patients.

3. Indications and contraindications for VA-ECMO

The major indication for VA-ECMO is cardiogenic shock as defined in the ELSO guidelines [14]. This includes inadequate tissue perfusion due to hypotension and low cardiac output despite volume repletion, inotropes, vasopressors, and intra-aortic balloon counterpulsation use. Common causes for cardiogenic shock are acute myocardial infarction (AMI), myocarditis, peripartum cardiomyopathy, acute decompensation of chronic heart failure, and postcardiotomy shock.

Septic shock is an indication in some centers. The guidelines on prognostication of survival without ECMO are based on the IABP score in postcardiotomy patients [15] and the Samuels score also in postcardiotomy patients [16]. In a retrospective analysis, Samuels et al. [16] showed that early insertion of mechanical support reduces multi-organ failure in these patients. In hospital mortality, correlates with increasing inotropic support needed to get patients off cardiopulmonary bypass following cardiac surgery. The combination of pharmacological criteria together with hemodynamic presentation should be used for mechanical support initiation in cardiogenic shock. Earlier institution of mechanical support devices tends to lower incidence of postoperative multi-organ failure and improve discharge rates [16].

The advantage of VA-ECMO is that it provides quick biventricular support and can be achieved at the bedside for poor oxygenation, biventricular failure, refractory malignant arrhythmias, and heart failure with severe pulmonary failure. VA-ECMO can be used as a bridge to recovery, AMI after revascularization, myocarditis, postcardiotomy shock, chronic heart failure, and non-revascularizable AMI.

ECMO can be used as a bridge to cardiac transplant as well as durable mechanical circulatory support: ventricular assist device (VAD) and the total artificial heart (TAH).

The absolute contraindications for VA-ECMO would be unrecoverable heart and the patient not being a candidate for cardiac transplant or VAD. Chronic organ dysfunctions such as emphysema, cirrhosis, and end-stage renal failure are all considered absolute contraindications. Compliance in terms of financial and medical strategies and cognitive, psychiatric, or social limitations are considered contraindications. Prolonged CPR without adequate tissue perfusion is also an absolute contraindication.

The relative contraindications for ECMO would be inability to tolerate anticoagulation, advanced age, and obesity. Advanced age is a gray area as there are no defined cutoffs due to lack of existing data in older patients.

4. Complications during VA-ECMO support

Complications encountered during ECMO support include lack of a fine balance between anticoagulation and bleeding, limb ischemia, disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), bleeding from a preexisting surgical site requiring reexploration, and progression of preexisting renal failure.

4.1 Anticoagulation and bleeding

Interaction of blood with non-endothelial surfaces leads to inflammation and prothrombosis. ECMO therefore leads to consumptive coagulopathy as well as a dilution of coagulation factors resulting in decreased fibrinogen levels. The inflammatory response secondary to ECMO gives rise to a hypercoagulable state, requiring anticoagulation to prevent thrombosis of the circuit. The delicate balance between adequate anticoagulation and bleeding complications presents one of the greatest challenges of ECMO therapy today. Different anticoagulation protocols are used across the centers. Uniformity in these protocols is lacking [17].

ECMO has historically been the mainstay of resuscitation in pediatric care. Adult ECMO protocols have hence evolved from the pediatric practice of anticoagulation in ECMO. Higher flow and larger cannula sizes in adult ECMO contribute less to turbulence, stasis, and thrombogenicity. Simple circuits with minimum number of connectors create less turbulence, while larger cannulas especially on the venous side reduce stasis and thrombogenicity, therefore requiring lower levels of anticoagulation. This suggests that anticoagulation protocols used in the pediatric population may not be optimal in adults.

Survival on ECMO appears to be more favorable in the younger population, and bleeding and coagulopathy appear to be the most common complications which raise the question if the coagulation system changes in its character and dimensions with advancing age. Interestingly, aging is accompanied by increases in plasma concentrations of factors VII and VIII and fibrinogen progressively [18, 19]. Coagulation cascade upregulation with age may increase thrombosis in pathological states demanding special attention when designing anticoagulation therapy for adult and especially older patients on ECMO.

Genetic polymorphisms and ethnic variations further complicate and influence drug metabolism and efficacy which need to be accounted for while developing anticoagulation protocols and selecting anticoagulants [20]. Clinical significance

and predictive value of hypercoagulability markers need to be defined in different age groups in prospective studies in order to be able to define optimal anticoagulation regimens. Research is needed in areas of optimizing anticoagulation protocols in adults with respect to age, gender, race, ethnicity, and technical aspects. If tailored appropriately adult ECMO therapy could probably achieve better success with far less aggressive anticoagulation than that used in the pediatric population.

4.2 Roller versus centrifugal pumps

Though centrifugal pumps are increasingly used, they are not without disadvantages. Centrifugal pumps are continuous flow pumps (CF pumps) and produce shear stress leading to acquired von Willebrand factor deficiency and bleeding complications. A recent retrospective analysis demonstrated an increased risk for nonsurgical bleeding (gastrointestinal, pulmonary, and neurological) with centrifugal pumps despite lower levels of heparin anticoagulation [21]. This study used patients supported on ECMO for 5 days for comparison of bleeding complications using centrifugal and roller pumps. The underlying etiology can be multifactorial but needs further research for specific delineation of inciting factors.

4.3 Limb ischemia

Femoral arterial cannulation carries an increased risk of profound distal limb ischemia. Some of the causes that lead to lower limb ischemia during ECMO support are acute embolism, dissection/perforation or rupture of the common femoral artery (CFA) or the iliac artery, thrombosis, pseudoaneurysm, hyperperfusion, and ischemia after decannulation usually due to distal embolization [22]. This problem has been solved to a large extent by prophylactically placing an ipsilateral perfusion catheter [22]. In a small study using 43 patients who underwent femoral artery cannulation, placement of a prophylactic superficial femoral artery [SFA] catheter in ten patients produced no limb ischemia. Of the rest of the patients (n = 33) who did not receive prophylactic SFA cannulation, seven patients had limb ischemia. Four of these patients underwent fasciotomy and decannulation leading to amputation in one patient. The three patients who received SFA cannulation for limb ischemia did not need amputation [23]. Foley et al. also showed that age was a predictor for limb ischemia [23]. Patients who developed limb ischemia were significantly younger than those patients without limb ischemia. This has been attributed to the size of the arterial cannula with respect to the femoral artery size in younger patients. CFA diameter was noted to increase with age. It was considered to be related to BSA and gender with increasing diameters found in males and those who have a larger BSA [24]. However, the data presented by Foley et al. found no correlation between the rate of limb ischemia and BSA, BMI, or size of the cannula as compared to the earlier literature [23, 24].

Accurate insertion of the arterial cannula in the CFA is of paramount importance to minimize risk of ipsilateral limb ischemia. One of the important aspects is to avoid improper retrograde SFA cannulation leading to significant flow limitation and in extreme cases to complete occlusion. Additionally, measurement of pressure in the SFA after placing the patient on ECMO support will identify the patients who actually need a catheter for antegrade perfusion [25]. Such an approach may reduce the extra effort and insertion of an additional catheter in all patients prophylactically.

Considering the limited data in the current literature, the use of prophylactic SFA cannulation in younger individuals may be a reasonable approach with or

without direct SFA pressure measurements especially if it can be done at the bedside. Duplex ultrasonography or direct SFA pressure measurements done at the time of ECMO placement may be an alternative to an early decision on which patients need the SFA cannulation. The existing literature does not seem to report a direct correlation with mortality in these patients which is another area of investigation that needs future attention.

4.4 Heparin-induced thrombocytopenia

Thrombocytopenia is a devastating complication in patients on VA-ECMO support. The etiology of platelet reduction in ECMO is still ambiguous. HIT has been considered one of the causative mechanisms. Current literature has very little to offer in this area. The incidence and mortality secondary to HIT in VA-ECMO patients is very poorly represented. In a recent retrospective study on VA-ECMO patients hospitalized for >3 days with high clinical suspicion of HIT and positive anti-PF4/heparin antibodies, the prevalence of HIT in patients on VA-ECMO support was estimated as 0.36%. Mortality rate was noted as 33.3%, which was not statistically different from the mortality observed in patients on VA-ECMO support without HIT [26]. HIT is a complication that appears to have a low prevalence; its effects are devastating if untreated. Bivalirudin and argatroban have been used to successfully treat this condition in VA-ECMO patients in small studies [27–29]. Further investigations in larger populations are required in this patient population for standardized regimens to be incorporated into the guidelines.

4.5 Disseminated intravascular coagulation

Extracorporeal cardiopulmonary resuscitation (eCPR) with VA-ECMO has become a reality in today's medicine to rescue patients in refractory cardiac arrest. DIC therefore becomes an important issue in this subset of patients who experience serious abnormalities in coagulation and thrombosis. Survival of adults supported by eCPR in adults is lower than that noted in patients supported on VA-ECMO [30]. In a retrospective analysis of eCPR patients it was noted they had consistently higher DIC scores and the mean DIC scores was significantly different between survivors and non-survivors [31]. It may be reasonable to use DIC scores in prognostication in these patients. Further studies are warranted in this area. Such prognostication remains very important as it can curtail excessive use of blood products.

5. ECMO as a bridge to transplantation

Cardiac transplant still remains the gold standard in treatment of end-stage heart failure. The scarcity of donors has led to the generation of a whole field of mechanical circulatory support devices which has brought in a new era in the treatment of advanced heart failure. The use of continuous flow LVADs as a bridge to transplantation (BTT) has become more popular and the mainstay of patients waiting on the transplant list [32]. More recently, VA-ECMO is being increasingly used as a rescue therapy [33, 34] However, this trend has now led to the use of ECMO as a direct bridge to transplantation in adults. This seems to be an attractive pathway for critically ill advanced heart failure patients waiting on the transplant wait list to get a heart very quickly it raises many questions about the feasibility of such an approach in the population. Though there is a very small portion of the

patients on the wait list who would be bridged directly on VA-ECMO to cardiac transplant, the lack of extensive literature and evidence for posttransplant survival of patients supported on ECMO makes this proposition questionable. Due to the large number of candidates waiting on the transplant list and too many high priority status 1A candidates in the wait list, the most recent organ allocation system has placed VA-ECMO bridge as the highest priority for cardiac transplant on the wait list [35]. This has a major disadvantage because of poor early and midterm posttransplant survival as compared to patients supported on CF-VADs [36]. It is therefore probably too early to use VA-ECMO as the highest priority for transplant organ availability/allocation.

BTT in the adult population has remained controversial despite small studies reporting varied survival rates posttransplantation in this population. The decision to use CF-LVADS as a BTT was based on various studies which showed improvements in functional status and quality of life in this population [37]. Such data is lacking in adults supported on VA-ECMO as BTT.

Therefore, the new system of allocation may reduce the transplant wait list mortality but may on the other hand increase the posttransplant mortality leading to a waste of organs in the setting of donor organ shortage. The most recent large retrospective analysis of the UNOS database showed a deceased survival in the early/mid posttransplant period [36]. Other studies from different countries have a wide variety of data which are limited.

The literature on use of VA-ECMO as a direct bridge to heart transplantation in adults is scanty. The use of VA-ECMO in posttransplant primary graft failure showed poor outcomes [38–40]. Since patients supported on ECMO are critically ill and the time to finding an organ is short, the extensive social and psychological evaluation required for transplant evaluation is not possible which could lead to suboptimal candidate selection.

Studies from France reported varying survival rates ranging from 51 to 70.4% at 1-year posttransplant in patients bridged on VA-ECMO [38, 41, 42]. Some of the caveats of these reports are the wait list mortality was not reported in the study by Jasseron et al. [38], while the duration of pretransplant ECMO support was not reported in the study by Rousse et al. [41] In the study Barth et al. [42], the survival was 100% at 1-year posttransplant though there were several adverse events and the study had a n = 8 with a mean age of 41 years. In a case series reported from Taiwan, 73% survived to hospital discharge in a cohort of 15 patients [43]. Mishra et al. [44] have reported a 1-year survival of 70%. A small study from Spain on posttransplant outcomes of patients bridged on ECMO showed no increase in mortality [45]. In France the special urgency wait list did improve the wait list mortality but also showed a significant increase in the posttransplant mortality [46].

6. Conclusions

The use of VA-ECMO as a technique for rescuing patients from cardiogenic shock is very attractive. However, considering the extensive set of complications and the mortality it brings with it makes it a less attractive option as a direct bridge to cardiac transplant. The literature currently on this subject is very scanty and limited to a few studies of small numbers of patients. The existing literature from France suggests a higher rate of posttransplant deaths even though the wait list mortality was reduced which does not seem to be an optimal way for organ allocation. In the light of present findings, further definitive research is needed for a consensus on the role of VA-ECMO as a bridge to cardiac transplant.

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Conflict of interest

Drs. Nandini Nair and Enrique Gongora have no conflict of interests to declare with relevance to this work.

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