REVIEW ARTICLE

Veno-venous extracorporeal membrane oxygenation for the treatment of respiratory compromise

Nnaemeka Ndubisi[1] · Victor van Berkel[1]

Abstract
Extracorporeal membrane oxygenation for the purpose of intervening upon profound cardiovascular or pulmonary compromise has proven to be a worthy intervention. Technological advancements have allowed this mode of therapy to become more effective and widespread. Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is a commonly used strategy to help manage patients with pulmonary dysfunction refractory to traditional management methods. This review intends to focus upon common indications and the clinical considerations for the institution of VV-ECMO as well as some of its known complications.

Keywords Extracorporeal membrane oxygenation · Respiratory compromise · VV-ECMO

Introduction

Extracorporeal membrane oxygenation (ECMO) is a short-term treatment modality used for therapeutic intervention, during a period of respiratory or cardiac failure, not amenable to traditional methods of care. The first successful use of extracorporeal circulation was in 1954 by Dr. Gibbons and his team during an open heart bypass operation [1]. This precursor machine ultimately led to the current-day cardiopulmonary bypass machine. The first documented case of ECMO use in respiratory failure was in 1972 [2]. It was also during this time period that the first randomized study investigating ECMO for pulmonary dysfunction was published [3]. The high mortality rates in that study prevented widespread adoption of ECMO as a support strategy. While ECMO use was used in certain specific pediatric populations, it wasn't until the H1N1 flu epidemic that it began regaining popularity in the adult populace [4]. One landmark trial in particular, the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial, demonstrated improved outcomes with ECMO in respiratory failure patients [5].

This, in addition to advances in ECMO technologies and the development of more efficient circuits [6], has played a role in its current-day wider acceptance.

The purpose of this review is to present evidence for the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO) for the treatment of respiratory compromise in addition to technical and practical aspects of its use.

Components

An ECMO circuit is comprised of a drainage and return cannula, blood pump, oxygenator, flow and pressure sensors, and heat exchanger [7]. The heat exchanger functions to cool or heat blood. Additionally, ECMO circuits also have venous and arterial points of access.

ECMO cannulation sites and cannula

ECMO can be instituted as veno-arterial (VA-ECMO) or veno-venous (VV-ECMO). Regardless of configuration, access is needed for both venous drainage and for blood return to the body, respectively. With VA-ECMO, when central cannulation is required, a thoracotomy or median sternotomy is performed [8]. This allows access to the central vessels, right atrium, or aorta. In peripheral VA-ECMO circuits, a venous cannula is placed in the femoral or jugular vein. Return is typically placed in the femoral or axillary

✉ Victor van Berkel
Victor.vanberkel@uoflhealth.org

1 Department of Cardiovascular and Thoracic Surgery, University of Louisville School of Medicine, 201 Abraham Flexnor Way, Suite 1200, Louisville, KY 40202, USA

artery [8]. For pulmonary issues, assuming adequate cardiac function, VV-ECMO is employed. This is routinely instituted percutaneously via the Seldinger technique and is often ultrasound guided [8]. Cannulas are wire reinforced to prevent bending. The correct placement of each cannula is confirmed via ultrasound, chest X-ray, fluoroscopy, or a combination of several techniques. In adult patients, the venous cannula is typically 50 to 70 cm with a diameter of 19 to 25 Fr [9]. In VV-ECMO, the drainage cannula is placed in the femoral vein and the return in the right atrium [9]. In our practice, as ECMO is often initiated under emergent conditions, we routinely first place both the drainage and return cannula in both the femoral veins, respectively. Thereafter, within 12–24 h, once the patient is stabilized, they are taken to the operating room for placement of a dual lumen cannula in the right internal jugular vein and both groin lines are removed. This type of access allows for drainage and return to take place via the same cannula and for patient movement following extubation.

Oxygenator

Typically, an oxygenator consists of receptacle comprised of two chambers which are divided by a semi-permeable membrane [10]. In one chamber, the patient's blood will flow and in the other fresh gas flows. The semi-permeable membrane is termed the oxygenation membrane, where gas diffusion takes place, allowing for the oxygenation of the drained venous blood and removal of carbon dioxide [10]. This process is driven by gradients which allows for the oxygenation of venous return blood and the evacuation of carbon dioxide. The partial pressure of blood in the chamber, and thus the degree of oxygenated blood that will be returned to the patient, is determined by the amount of oxygen in the fresh gas flow which can be controlled via the ECMO circuit settings [10]. Conversely, the removal of carbon dioxide is driven by the gas flow rate, so increasing the flow will lead to more CO_2 removal from the blood [10].

Blood pump

In an ECMO circuit, blood flow is driven by the blood pump. The popularity of roller pumps has given way to centrifugal pumps, a newer technology which uses a magnetic field to generate the force used to circulate blood [11]. This leads to decreased compression of blood, as compared to a roller pump, and thus a lower degree of inflammatory system activation [12]. Regardless of pump type, it is important that ECMO circuits have an alternate way for circuits to continue flowing in the case of patient transport or when a power failure occurs. This is often made possible via a battery and/or external hand crank.

Support for acute respiratory infection (CESAR trial H1N1, COVID)

It was during the H1N1 flu epidemic in 2009 that ECMO, or more specifically VV-ECMO, began gaining acceptance for the treatment of lung disease. The studies published before this time, however, were largely observational and sometimes contained conflicting results [13, 14]. As a result, many remained skeptical of this treatment modality. Further, it had not survived the rigors of a randomized study which would be required for more widespread acceptance. This void in the literature ultimately leads to the CESAR trial [5]. This randomized study, published in October 2009, demonstrated a significant improvement in death or severe disability at 6 months compared with conventional mechanical ventilation. Even with its increasing acceptance, some remained reluctant to adopt ECMO citing the percentage of patients in the CESAR study ECMO group who did not undergo ECMO (24%) and the absence of lung-protective ventilation in the control group. Another more recent trial performed in 2017, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial [15], showed that although there was no difference in the 60-day mortality primary outcome, a secondary outcome of death or treatment failure (which was defined as death or crossover to ECMO in the control group) was significantly improved in the ECMO cohort. Crossover to emergency ECMO in the control group was 28%. Moreover, the EOLIA study protocol included the use of lung protective strategies, prone positioning, as well as neuromuscular blocking agents before and after study enrollment.

The initial wave of the coronavirus disease 2019 (COVID-19) pandemic saw an intensive care unit admission rate of 21%, with 69% of these critical care admissions ultimately requiring mechanical ventilation [16]. Initial published data revealed high mortality rates associated with the use of ECMO in the COVID population and some providers deemed there was not enough evidence to support its use in this group of patients [17, 18]. In 2020, however, the Extracorporeal Life Support Organization (ELSO) registry published a cohort study of 1093 patients aged > 16 years who underwent VV-ECMO for respiratory insufficiency secondary to COVID-19. It was found that the estimated cumulative incidence of in-hospital mortality 90 days after the initiation of ECMO was 37.4% [19].

This mortality rate is consistent with that of which was seen in the CESAR study and EOLIA study, at 37% and 35%, respectively. With these data in mind, ECMO became a consistent tool in the armamentarium of those treating patients suffering from the acute pulmonary effects of COVID-19. Table 1 summarizes the inclusion and exclusion criteria suggested by the ELSO, ECMOnet, CESAR, and EOLIA studies.

Table 1 Indications for ECMO (VV-ECMO)

	ELSO [20]	ECMOnet [21]	CESAR [5]	EOLIA [13]
Indication	Mortality > 80% P/F < 80 Fi > .90 Murray score 3–4	OI > 30 P/F < 70 PEEP 15 ≥ for patients in ECMO center pH < 7.25 × ≥ 2 h	Potentially reversible respiratory failure Murray score ≥ 3	P/F < 50 Fi > 0.8 × > 3 h P/F < 80 Fi > 0.8 × > 6 h pH < 7.25 for > 6 h (RR increased to 35) adjusted to keep Pplat < 32
Consideration for ECMO	Mortality > 50% P/F < 150 Fi > 90 Murray score 2–3	P/F < 100 PEEP ≥ 10 patients awaiting transfer to ECMO center	Murray score ≥ 2.5	
Contraindication	Condition incompatible with life pre-existing conditions Age Futility Mechanical ventilation > 7 days	Contraindication to anticoagulation Severe disability Mechanical ventilation ≥ 7 days	PIP > 30 Fi > 0.8 Mechanical ventilation > 7 days Contraindication to anticoagulation Contraindication to ongoing treatment	Mechanical ventilation > 7 days Age < 18 years Pregnancy BMI > 45 Hx of heparin-induced thrombocytopenia Chronic severe respiratory disease SAPS II > 90 Moribund Malignancy-predicted survival < 5 years ECMO cannulation not possible

Support for post-trauma (non-infectious) ARDS

The incidence of severe trauma leading to acute respiratory distress syndrome (ARDS) is roughly 10% [22]. This most commonly occurs after mechanisms including blunt thoracic trauma accompanied by severe pulmonary contusion, hypovolemic shock prompting massive transfusion, and flail chest [23].

The first described use of ECMO in the post-traumatic patient was published in 1972 [2].

Trauma patients are typically younger and healthier than non-trauma patients developing respiratory failure. These baseline characteristics are partially responsible for a favorable prognosis in trauma-related ARDS. Overall, although it is difficult to make direct comparisons, the data suggests that post-trauma VV-ECMO survival rates are non-inferior to those of adult patients, ranging from 50 to 79% [22, 24]. One study sought to determine if VV-ECMO improved survival in trauma patients suffering from acute hypoxemic respiratory failure and demonstrated that it was independently associated with improved survival. It was also seen that blood transfusions increased, and more bleeding complications were noted as a result [25].

Bridge to transplant

Due to supply and demand mismatches, organ availability continues to be a problem in lung transplantation. This is associated with increased wait-list times and the reported 10–20% mortality rate for patients while waiting [26]. Moreover, mechanical ventilation has been shown to be an inadequate bridging primary strategy [27]. The first reported case of ECMO as a bridge to lung transplant was in 1977 in a patient with post-traumatic respiratory failure who subsequently underwent bilateral lung transplantation [28]. The International Society of Heart and Lung Transplantation recommends ECMO as a bridge to transplant in young patients, without multiorgan dysfunction, with good rehabilitation potential. Patient selection in these circumstances is critical. In recent literature, the median duration of an ECMO bridge is 2–17 days [29, 30]. ECMO-associated bleeding is the most frequently reported complication [31–33]. Outcomes, however, have been shown to be good, with survival to lung transplantation ranging from 56 to 89% [31, 33, 34]. These survival findings are favorable given that patients in this population, often presenting in extremis, would likely expire prior to transplantation without the benefit of this treatment modality.

Support for post-transplant primary graft dysfunction (PGD)

PGD is defined by the International Society of Heart and Lung Transplantation (ISHLT) as a decreased partial pressure of oxygen (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) ratio and the presence of diffuse infiltrates on thoracic

imaging without other identifiable cause [35]. This devastating clinical circumstance is thought to occur in 15–30% of all lung transplants (LTx) [36, 37]. ECMO has been shown to improve survival in post LTx patients with PGD and, as such, PGD is the most common indication for post-transplant ECMO [38]. In order to minimize the harmful effects of elevated airway pressures, or high oxygen concentrations, prompt ECMO initiation has been recommended in the setting of PGD when peak airway pressures reach 35 cm of H_2O or when FiO_2 surpasses 60% [39]. If the modality is deemed necessary, delaying ECMO initiation greater than 48 h has been associated with worse outcomes. [40]

Clinical considerations with VV-ECMO

Mechanical ventilation management

One of the primary advantages of VV-ECMO is the reduction of both ventilator intensity and dependence. Lung protection strategies including plateau pressures < 30 mmHg, and tidal volumes $6 \leq$ cc/kg, should be followed so as to decrease the risk of known ventilator-associated complications [41]. Additionally, patients should be extubated as appropriate. If unable to extubate, early tracheostomy should be considered as this helps to wean sedation, improve oral care, and reduce the incidence of vocal cord damage as a result of trans laryngeal endotracheal intubation [42].

Acute kidney injury

The overall incidence of acute kidney injury (AKI) in patients on VA and VV-ECMO is reported at 26–85% [43]. This wide range results from patient baseline characteristics, clinical circumstances, and differences in AKI definition. An AKI is also more common in VA-ECMO than VV-ECMO (61% vs 46%) and is most often present on the day of cannulation [44, 45]. Regardless of ECMO configuration, the underlying mechanism for the disruption of kidney function is theorized to be related to the systemic inflammatory response, intravascular volume depletion, hypotension, tissue hypoperfusion, and hemolysis [46]. For those requiring renal replacement therapy, continuous renal replacement therapy (CRRT) is recommended [47]. Consensus as to when to initiate CRRT, early or late, has not been reached [47].

Bleeding and intracranial hemorrhage

The risk of any bleeding with ECMO is reported to be as high as 29% [48], with a 10% risk of major bleeding, and a 4–10% risk of intracranial hemorrhage [49, 50]. There are many postulated reasons as to why bleeding is thought to

be an issue in ECMO patients. First, ECMO circuits confer an elevated risk of thromboembolism due to blood exposure to non-biologic circuit and the non-pulsatile blood flow. This can lead to clot formation within the ECMO circuit and ultimately prompt a complete exchange of ECMO circuit components in 10–16% of cases [51]. As a result, ELSO endorses, in its latest international guidelines, the practice of an unfractionated heparin protocol to minimize the risk of circuit thrombosis although they also maintain that there is currently a paucity of evidence to guide optimal anticoagulation management in adult ECMO patients [52]. Furthermore, the most recent ELSO guidelines also state that the tendency towards less (lower or no) anticoagulation is potentially safe and feasible. As this continues to be an evolving topic, at our institution, we currently adhere to prior ELSO recommendations [53] where patients usually receive an initial unfractionated heparin bolus of 50–100 units per kilogram at the time of cannulation with an infusion then continued during the ECMO course. This infusion is initiated at dose of 7.5–20 units/kg/h in adults and titrated to maintain an activated partial thromboplastin time (PTT) of 60–90 s. This lab is typically drawn every 6 h. There are circumstances where anticoagulation is held, namely bleeding or profound coagulopathy as evidenced by lab values. At our institution, if the patient's flow on ECMO is > 2 L per minute, then the withholding of anticoagulation is considered safe.

Accordingly, when anticoagulation is administered, the risk of bleeding increases. Furthermore, ECMO patients are commonly critically ill or in the postoperative period, both known conditions for increased risk for bleeding complications [54, 55]. Intracranial hemorrhage (ICH) is the most dreaded complication of extracorporeal life support. In some cohorts, it has been reported as the leading cause of death in VV-ECMO patients [56]. In the ECMO population, ICH is difficult to diagnose due to the sedation that is often required for these patients. Computed tomography imaging is the most commonly used tool to diagnose this complication but patient instability can delay or prevent this assessment [57]. The implications of this complication are devastating as the ELSO registry data reports that only 26% of VV-ECMO patients who develop ICH survive to discharge [58].

As VV-ECMO is a mechanism of support that can keep patients alive despite un-survivable injuries, determining when continued therapy is futile is a difficult process. This determination should be made as a collaborative discussion amongst surgeons, intensivists, and any other involved patient care team. If no meaningful recovery can be expected, providers should empathically state this to family, and then allow the family time to process this information, before recommending withdrawal of VV-ECMO therapy and transition to comfort care, if comfort care is thought possible [59].

Conclusion

VV-ECMO is a form of mechanical circulatory support that has been shown to be effective in temporarily managing patients with profound respiratory failure. It is important, therefore, that providers managing these patients are knowledgeable of its components, indications for use, patient populations demonstrated to benefit, and its clinical considerations, including common complications.

Declarations

Ethical statement This document is a review of the current literature, without involvement of new human or animal subjects. As such, there is no need for EC approval.

Informed Consent Not applicable as there is no patient identifying material.

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Human and Animal Rights Statement Not applicable.

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