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Surging Role of Extracorporeal Membrane Oxygenation in Refractory ARDS Due COVID-19 and In-depth Review of Existing Applications

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Abstract

Introduction: Extra Corporeal Membrane Oxygenation (ECMO) is a device applied to maintain cardiopulmonary support in patients in whom there is a failure of the cardiopulmonary function to maintain perfusion to vital organs. Previously, ECMO was used in pulmonary embolism, cardiogenic shock, myocarditis, and heart failure cases. Its use in refractory acute respiratory distress syndrome (ARDS) in coronavirus disease 2019 (COVID-19) has increased, but the data regarding its safety, efficacy, and mortality benefit remains unclear. The focus of our review is to further expand on these areas and outline the indication, techniques, and complications associated with its use.

Methods: We did an extensive search of various databases such as PubMed, Cochrane, ScienceDirect, and Jama Network and studied 41 papers, including free full articles such as systematic reviews, meta-analyses, and clinical trials published within the past five years.

Results: Implementation of ECMO is advantageous when the PaO2/FiO2 is in the range of 100 to 150 mmHg. For COVID-19 patients, the most appropriate approach is to drain from a femoral venous cannula and thread it to the inferior vena cava just 1-2cm below the cavoatrial junction. It was seen that the most common complication of ECMO use is coagulopathy. Limb ischemia had a variable incidence from 10 to 70% and is more common in venous-arterial ECMO.

Conclusion: ECMO is lifesaving in a highly selected group of patients to prolong survival, reduce complications and provide a good prognosis in terms of mortality. To prevent circuit thrombosis, anticoagulation is key, and understanding feasible intra-atrial communication sites, such as a patent foramen ovale or atrial septal defects, is beneficial to mitigate the risk of stroke and cutting down consequences of thromboembolism.

Keywords: ECMO", "extracorporeal membrane oxygenation," "ECLS", "extracorporeal life support", and "ARDS

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Background

Understanding ECMO aka ECLS functioning and applications

Extracorporeal membrane oxygenation (ECMO), alternatively referred to as extracorporeal life support (ECLS), is a rescue therapy used to stabilize critically ill hemodynamically compromised patients. It is a method of extracorporeal circulation and ventilation support in which the entire cardiopulmonary function is shifted to maintain oxygen supply to the organs while managing the primary illness [1].

ECMO is a very resource-intensive and effort-intensive intervention, usually reserved for highly selected patients who have failed to respond to medical therapy and mechanical ventilation in conjunction with cardiopulmonary resuscitation (CPR) [2, 3] Thus, its use is not recommended for patients with a poor chance of survival [3].

The indications for its use include cases of cardiogenic shock, massive pulmonary embolism, calcium channel overdose, and as a bridge for a left ventricular assist device (LVAD) [4]. ECMO was previously used in severe cases of H1N1 and Middle Eastern Respiratory Syndrome (MERS), and its role in COVID-19 is increasingly being recognized [5].

Analyzing ECMO and patient factors

ECMO provides a means of life support for patients who require respiratory and/or cardiac support. In a systematic review performed by Hu BS et al., ECMO was proven to rescue patients having refractory hypoxemia. However, it was difficult to determine its usefulness in reducing COVID-19 related mortality rates [1].

The role of this technique in reducing mortality rates in debilitated patients is still being explored. The indication is expanding, and it is now widely used in children and adults to aid in cardiopulmonary resuscitation [6].

Nonetheless, patient outcomes depend on multiple factors such as the duration of the treatment, the disease severity, the training of the medical professionals, and the equipment used [1]. Our review will outline the various indications, technicalities, and complications along with the recent trends of its use in the current pandemic.

ECMO: Indications and contra-indications

The most used ECMO methods are veno-venous extracorporeal membrane oxygenation (VV-ECMO) and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) [6]. The basic difference between them is the types of cannulae and the location of their placement [7].

Understanding the Role of ECMO in Cardio-Respiratory division

V-V ECMO primarily supports lung functions. Only a single cannula with two channels, side by side, is placed in a large vein, most commonly the neck vein, which allows the ECMO pump to draw blood out via one channel and back into another. Sometimes, the surgeon might decide to place the cannulae in the veins of the lower extremities [7].

V-A ECMO assists both heart and lung functions. Two cannulas are used, one is placed in a large vein, and the other is placed in a large artery so that blood can be taken out of a vein and returned into an artery. V-A ECMO is compared to the heart-lung machine [7].

Indications of VV-ECMO

The Extracorporeal Life Support Organization (ELSO) reported three indications for VV-ECMO, such as patients with viral pneumonia, postoperative or trauma-related to acute respiratory distress syndrome (ARDS), and bacterial pneumonia. According to the report, each group was given VV-ECMO for a number of hours, and they showed good survival scores [6].

ECMO and In – depth analysis of EOLIA trial

EOLIA trial, a randomized multicenter international trial, outlined the indication for VV-ECMO for patients who have failed to respond to adjunctive therapies and mechanical ventilation. The mortality at 60 days was the primary endpoint, and the inclusion criteria are listed in Table *1* [8]. They found a mortality rate of 35% (44/124 patients) in the ECMO group and 46% (57 of 125 patients) in the control group [8].

Table 1: VV-ECMO Criteria: EOLIA trial

Age	>18 years old
Receiving mechanical ventilation	< 7 days
PaO2:FiO2 (ratio of arterial O2 tension to fraction of inspired O2)	< 50 mmHg for > 3 hours
PaO2:FiO2	< 80 mmHg for > 6 hours
Arterial blood PH with PaCO2 > 6 hours	< 7.25 and > 60 mmHg, respectively

VV-ECMO: veno-venous extracorporeal membrane oxygenation; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen; PaCo2: partial pressure of carbon dioxide.

Indications of VA-ECMO

The main indications for VA-ECMO are cardiomyopathy, cardiogenic shock, myocarditis, and congenital heart disease showing 51%, 42%, 65%, and 37% of survival rates, respectively [6]. According to Dangers et al. and Ontario health technology assessment, this method is also indicated as an interface in left ventricular assist device and heart transplants, as well as in cardiogenic shock, refractory cardiac arrest, and acute decompensated heart failure with a Sequential Organ Failure Assessment (SOFA) score <11 [9,10]. Also, this mode still is the most ECMO method used for neonates with respiratory failure; however, they have most higher survival rates with VV-ECMO than those with VA-ECMO [6].

To support cardiogenic shock and cardiac arrest, the implantation can be using a surgical or percutaneous procedure. Echo-guiding for percutaneous cannula insertion has been described with a lower risk of vascular complication. Martin-Tuffreau AS et al. demonstrated 100% of the success of vessel cannulation with this method of implantation [5].

Contraindications of ECMO

ECMO is contraindicated in patients with advanced age, significant co-morbidities, and multiple organ failure. However, renal failure is not considered a contraindication for ECMO [11]. Other potential contraindications can be immunocompromised status, ongoing cardiopulmonary resuscitation (CPR), and the inability to receive systemic anticoagulation [12].

Technical Management

ECMO should only be performed by trained and experienced clinicians. The standard circuit comprises a blood pump that drains the body's blood and passes it through the external oxygenator and heat exchanger.

Carbon dioxide is removed when the blood gets saturated. This blood is then incorporated back into the body through the return cannulae [7] [13] (Fig.1)

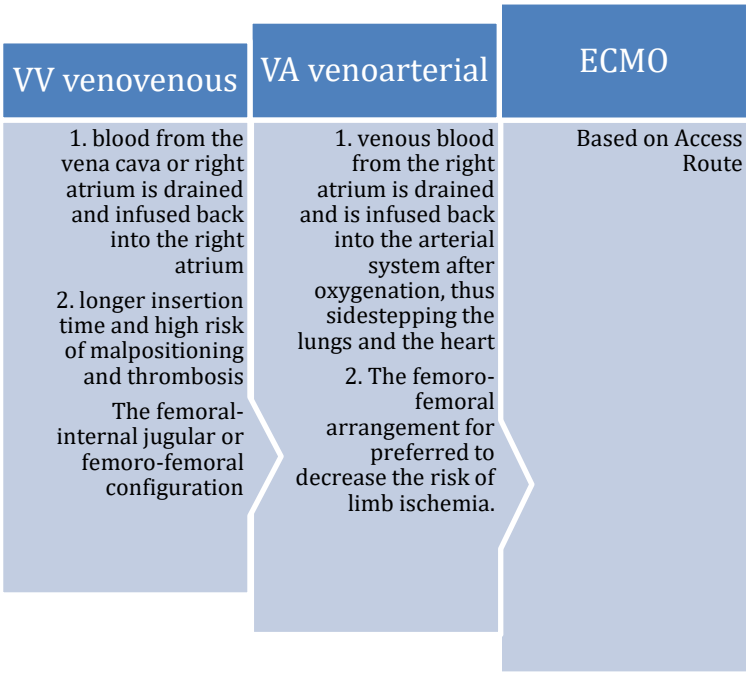

Figure 1: Types of ECMO

Role of ECMO in COVID-19 management

The internal jugular vein near the superior cavoatrial junction is where the return cannula should be placed [7].

Another approach is the insertion of a dual lumen single catheter where the single catheter is percutaneously inserted through the internal jugular vein, while the two drainage ports utilized are in the inferior and superior vena cava. Blood drawn from these ports flows into the oxygenator and returns through the single port near the tricuspid valve. These catheters allow increased patient mobility [14].

Confirmation of cannula position can be achieved by chest x-ray or transthoracic or transesophageal echocardiography (TEE), although TEE examination is not appropriate for COVID-19 patients due to aerosol generation [14,15].

VA-ECMO is discouraged as a protective strategy, especially if patients requiring VV-ECMO are stable on inotropes with no cardiac dysfunction.

Instead of a double-lumen cannula, the three separate single-lumen cannulas are recommended for VA-ECMO [13]. In VC-ECMO central arrangement, while the drainage cannula is in the right atrium, the return cannula is inserted in the aorta (ascending segment). However, in the peripheral arrangement, the blood flows through the jugular or femoral veins and returns through the axillary, femoral, or carotid arteries. Thus, the exclusion of pulmonary circulation is characteristic of VA-ECMO [7].

Use of ECMO in Refractory ARDS due COVID-19

About 14% of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) go into a more serious infection that requires oxygen support and hospitalization, with an overall 5% that admit to the ICU [16]. For the COVID-19 related acute respiratory distress syndrome (ARDS) treatment, WHO recommended the use of venovenous ECMO only in expert centers [16].

In ARDS, this device should be considered when prone position ventilation and mechanical ventilation for lung protection strategies fail to correct the respiratory compromise. This strategy includes maintaining a tidal volume ≤ 6ml/kg, plateau pressure <30cm H20, PEEP ≤ 10 cm H20 [17].The indications for these patients include PaO2/FiO2 < 100 mmHg, or > 600 mmHg of P(A-a)O2, more than 35 breaths per minute of ventilator frequency, < 7.2 pH, and >30 cmH20 of plateau pressure, age 65 years and above, and < 7 days of use of assisted ventilation [8].

This strategy minimizes pressure for respiratory drive along with inhibiting inflammation that reduces damage to lungs and other organs [18,19].

In a multicentre study, Yang et al. describe their experience with 21 patients that received ECMO for severe ARDS in COVID-19 cases in Wuhan, China. The study showed a 43% survival rate for patients that received the ECMO intervention, in contrast to 37% of patients who received only mechanical ventilation without ECMO. Those patients who had lower PaCO2 and higher pH prior to the intervention had increased chances of survival. These findings reveal that a previous degree of lung damage may predict death in these cases, as hypercapnia is due to the worsening dead-space fraction in ARDS [19].

Due to the high infectivity of novel coronavirus, the use of ECMO is a high-risk proposition because, in addition to body fluid splashes, including secretions and blood causing infection, it also has its unique procedural challenges that require highly skilled personnel. [17,20] To minimize the probability of spreading infection and reduce ECMO complications, extensive precautions are required, such as placing patients under negative pressure rooms, restricting staff movements in and out of the rooms, and all staff supplied with level 3 biosafety protection. The primary mode should be VV- ECMO, although, in patients that develop myocarditis, veno-arterial ECMO with a mode that assists the heart may be used [17]. At this point in the coronavirus outbreak, we are at a stage where resources for ECMO are more evolved, and there is substantial data to support the effectiveness of its use in patients with severe ARDS bearing in mind the precautions and minimizing the complications [21].

ECMO in Pediatrics Division

According to ELSO, while using ECMO in neonates, clots can be challenging as it may lead to respiratory failure as e a mechanical complication. Neurologic complications also arise and, according to the 2016 ELSO report, the incidence of intracranial hemorrhage (ICH) was found to be 7.6% in these cases. Hypoxemia and acidosis along with organ failure increase the risk of these complications [22]. However, in a meta-analysis, when ECMO was used to resuscitate children, a 59% survival rate was seen with central cannulation [23]. The 2020 Pediatric Respiratory ELSO Guideline reports 73% survival rates for ECMO use in neonates with severe respiratory disease [24].

Complications

Although the most significant predictor of outcomes for ECMO use is prompt initiation of this technology, the risks and benefits should be carefully weighed as it is associated with various adverse events [25].

Thrombosis is a common event in patients undergoing ECMO. Due to the use of cardiac circuits, there is an increased risk for clots and bleeding complications [26,27]. To prevent this, the standard procedure is to start a patient on continuous infusion of unfractionated heparin for anticoagulation before ECMO is initiated. Bemtgen et al. in their study found that COVID-19 patients were more likely to have thrombosis [28].

Malfunctioning of the cardiac circuit and migration of canula can occur. COVID-19 patients using ECMO also developed complications such as brain hemorrhage, cardiac shock, and liver failure [29]. Removing

directly venous or arterial cannula inserted by percutaneous access and making a topical pressure might be a good strategy to control the bleeding [30].

A bubble sensor device can be added to the ECMO circuit to pause the pump in the presence of bubbles into the tubing, helping the ECMO professional remove the air immediately and prevent gas embolism [31]. In addition, the prone position might be related to lower mortality [11].

In a study by Chen et. al, around 20% presented coagulopathy, and it was seen that in critical illnesses, there is evidence of coagulopathies to various extents. Multiple mechanisms can lead to thrombosis in ECMO stem from activation of the coagulation pathway due to the inflammatory process that activates platelets or interactions and shear stress between the foreign material and blood cells. There is also acquired antithrombin (AT) deficiency due to heparin use [27,28].

Returning coagulation to an average level as much as possible when the bleeding starts by decreasing the anticoagulant infusion, transfusing platelets until it counts higher than 100,000 should be considered to manage the bleeding. Antifibrinolytics can be given to the patient if fibrinolysis is suspected or confirmed [30].

Limb ischemia can be prevented by the use of a reperfusion catheter [32,33].

A prospective study conducted by Falcoz PE et al. reported 35.3% of the patients requiring blood transfusion, and one (5.8%) developing hemorrhagic shock [27]. Common hemorrhagic sites are the respiratory tract, cannula, skin, oronasal mucosa, GI tracts, and lungs. The presence of hematologists in the multidisciplinary team to indicate adequate anticoagulation therapy supplementation should be maintained while using ECMO therapy. The study of whole blood, von Willebrand factor, and platelet aggregation assay could be a good tool to recognize those with an elevated risk of coagulopathy related to ECMO. Thrombus in cannulas formed after removal can also increase morbidities [27] [30].

Infection is another significant complication related to ECMO, the longer the use, the greater the risk for infection. Therefore, a sterile environment (operating room, cardiac catheterization suite) must be set up, and antibiotic prophylaxis should be continued after initiation of VA-ECMO [25].

Moreover, adverse events or complications during ECMO transports occur in 31.7% of cases. The interventions must be made within seconds when needed and require a highly trained mobile team [34].

Discussion

Extracorporeal membrane oxygenation is a prominent intervention for critically ill patients and has restricted indications. It is not exempt from complications, and the most common are thrombotic phenomena and bleeding [27]. Previous studies demonstrated that critical illness patients with H1N1 decreased mortality by 50% when treated with ECMO [35]. In a cohort study by Hayanga et al., with 15,829 adult patients, the mean age of ECMO use was found to be 52.8 years. The most common indication for use of ECMO was shock (post cardiotomy, 39% and cardiogenic, 37%), respectively [36].

The use of ECMO was found to be associated with elevated hospital charges [36]. A study analyzed costs and found a range between US$91,732 and US$143,729 in post cardiotomy patients, and between US$205,080 and US$331,355 in heart or lung transplantation patients under ECMO, respectively [37]. The highest costs in the US study in the youngest patients with cardiogenic shock were explained by the most extended length of stay in the hospital [37]. In hospitals with high volume, the costs are higher than in those with medium- and low-volume. For example, the ECMO system spent 19.5% on consumables and maintenance and 11% on personnel, according to Buiskova et al. on ECPR study. In another study, the authors found that 68% of the total cost related to ECMO for survivors was due to days in ICU and hospital [37].

As reported in April 2021 by ELSO, the use of ECMO proliferated, showing a total of 151,683 runs in 492 centers compared with 347 centers in 2015, expressing a growth of 41% in the last five years. However, this device's availability was not seen in developing countries such as Brazil, China, and India, which have less than 11% of the total runs altogether [38]. Since its development in the 1960s, according to the last annual report of 2020, 135,000 patients had this intervention done on them, and this number has significantly increased due to the advent of COVID-19. Recent data from ELSO live (accessed on October 14, 2021) counted 9,748 patients with confirmed COVID-19 supported by ECMO worldwide with 64% being in North America [39].

Sklar et al. analyzed 18 studies, including 646 patients with ARDS, and found that the total duration of VV-ECMO was at a range of 4 - 20 days. The bleeding rate was 16%, and the rate of thrombosis was 53% [36]. For patients who require milder anticoagulation therapy to decrease thrombosis risk, the flow through the circuit can be increased to a maximum [40].

Mortality during VV-ECMO varies and has been reported from 0 to 50%. In one study, 29% (186 cases) deaths were recorded when considering all studies [33]. Despite the recent advances in ECMO technology, the efficacy of VV-ECMO in severe ARDS remains controversial, hence further studies are needed [8].

There are 112 clinical trials that are active to better understand the indication and use of ECMO. Nine are specific to study effectiveness in COVID-19 positive patients [41]. As a limitation of this study, the high costs of the intervention and the high mortality rate seen in these patients make it a questionable intervention in terms of sustainability, but further research is required to weigh the risks and benefits.

Conclusions

ECMO had demonstrated paramount potential to support and keep patients alive while the native lungs and hearts are recovering. It is indicated in neonates to the elderly and is specially designed to prolong survival, reduce complications, and improve prognosis in debilitating conditions. However, this supportive method needs exceptional management in institutions with appropriate resources such as equipment and workforce. Furthermore, apart from high costs, complications such as thrombosis and bleeding can arise. So, the risk and benefits should be properly weighted before starting this intervention, and appropriate precautions must be taken to prevent infection and other complications.

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