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Review

A Brief Overview of the Use of Extracorporeal Membrane Oxygenation (ECMO) in COVID-19 Patients with Severe Acute Respiratory Distress Syndrome (ARDS)

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ABSTRACT

Background

A serious complication of coronavirus disease 2019 (COVID-19) is acute respiratory distress syndrome (ARDS). Hypoxemia refractory to traditional management, including invasive positive pressure ventilation, is not uncommon with COVID-19. It can lead to circulatory failure necessitating the use of mechanical circulatory support devices, specifically extracorporeal membrane oxygenation (ECMO).

Aim

This paper provides a brief update on the use and indications of ECMO for adult patients with COVID-19 around the world.

Methods

We conducted a rapid umbrella review on the use of ECMO in treating COVID-19-related ARDS (CARDS), as well as current indications and contraindications for the initiation of ECMO. We reviewed the use of venovenous (V-V) ECMO and veno-arterial (V-A) ECMO in CARDS.

Findings

V-V ECMO is the primary ECMO mode employed in the majority of the patients who required ECMO support for CARDS. Although the duration of V-V ECMO in COVID-19 was longer than the V-V ECMO in non-COVID-19 patients with ARDS, the mortality rate appears similar. Meta-analyses reviewed reported an in-hospital mortality rate ranging from 37% to 49% for COVID-19 patients who required V-V ECMO.

Conclusion

The survival benefit of ECMO in COVID-19 patients with severe cardiopulmonary failure is not clearly established, but V-V ECMO may be considered in adults with COVID-19 and severe cardiopulmonary compromise when resources are available. V-A ECMO may be considered in COVID-19 patients with severe cardiac failure, but limited data are available on survival benefits.

Keywords: COVID-19, ARDS, CARDS, ECMO

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-Co-V2), commonly known as coronavirus disease 2019 (COVID-19), is caused by a single-stranded RNA virus that is closely related to bat coronaviruses (Zhou et al., 2020). COVID-19 infection

demonstrates a degree of hypoxia disproportionate to the compliance of the respiratory system (Gattinoni et al., 2020). At the beginning of the pandemic, as much as 20% of the patients hospitalized for COVID-19 required intensive care unit (ICU) admission for the management of severe hypoxia (Guan et al., 2020), and a large proportion of these patients who required mechanical ventilation developed acute respiratory distress syndrome (ARDS) (Estensorro et al., 2022).

ARDS in COVID-19 and Initiation of ECMO

A diagnosis of COVID-19 ARDS (CARDS) is made once a patient who has COVID-19 meets the Berlin ARDS diagnostic criteria (ARDS Definition Task Force, 2012). The criteria involve hypoxic respiratory failure of acute onset, presenting within one week of onset of respiratory symptoms, along with bilateral airspace disease on chest imaging not fully explained by lung collapse, nodules, or effusions, and heart failure is excluded as the primary cause of the underlying respiratory failure. ARDS is categorized as severe when the arterial oxygen partial pressure (PaO2) to fractional inspired oxygen (FiO2) ratio is less than or equal to 100 mm Hg (Ferguson et al., 2012). The clinical decision on when to initiate ECMO in patients with CARDS is often difficult. Data on the utilization of ECMO in CARDS, along with the indications and contraindications for initiating ECMO, would give an insight into the scope of utilization of ECMO in CARDS.

PURPOSE

The purpose of this paper is to provide a brief overview of the operation of ECMO and clinical considerations to support decisions to initiate ECMO in patients with CARDS.

Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) involves using a very sophisticated and complex machine that replaces the function of the lungs or lungs plus the heart, while an individual's blood is circulated outside his/her body, implying the term extracorporeal. The machine is similar to the heart-lung machine often used intraoperatively for on-pump cardiac surgeries, as well as for heart transplants. The patient's blood is pumped out of the circulatory system into an ECMO circuit where it flows through a system of tubes, filters, and membranes while removing carbon dioxide and adding oxygen to the patient's blood before it is returned to the circulatory system of the patient. ECMO is a temporary measure, often used for a few days to weeks until the lung/cardiac function recovers or until a transplant or other durable devices are available (Ungvarsky, 2022).

There are two main ECMO circuits used, veno-venous (V-V) ECMO and veno-arterial (V-A) ECMO. When a V-V ECMO circuit is used, the patient's blood flows into the ECMO circuit from a major vein in the patient's body and is returned to one of the larger veins in the patient's circulatory system. A V-V ECMO circuit is

used when the clinical problem arises mainly from a non-functioning lung. A V-A ECMO circuit implies taking venous blood from the patient to the ECMO circuit and returning it to the patient's arterial system. A V-A ECMO circuit is primarily employed when both the lungs and heart of a patient exhibit failure (Ungvarsky, 2022).

METHODS

Data were obtained from data published by Extracorporeal Life Support Organization (ELSO) on their website in combination with a rapid umbrella literature review. ELSO is a non-profit international consortium including researchers, healthcare organizations, and business associates, originally founded by Robert H. Bartlett, MD, who is recognized as the pioneer in ECMO utilization. Cases of ECMO use in COVID-19 reported by ELSO include ECMO-supported cases of confirmed or suspected COVID-19 cases reported by different ELSO chapters. Year-to-date data were obtained for adult ECMO runs for COVID-19 in North America and the rest of the world. A literature search was done to identify the available original research studies on the use of ECMO in COVID-19 in adults worldwide from the beginning of the pandemic till date.

A literature search was performed using the following major electronic databases; the Cochrane Library, ProQuest, PubMed Central, and Medical Literature On-Line (MEDLINE). The inclusion criteria were reviews, systematic reviews, retrospective studies, and observational studies, mainly multicentered studies from all over the world, published in English that reported the use of ECMO in COVID-19 and the outcomes of ECMO use in COVID-19. Only full-text and peer-reviewed articles were included in the literature search. The search terms used included COVID-19 and ARDS; ARDS and ECMO; ECMO use in COVID-19; COVID-19 registry; indications for ECMO use in COVID-19; and data on ECMO in COVID-19. The Boolean operators such as "AND," and the truncation symbol asterisk was also employed for searching the articles. Any case studies, single-centered studies, or articles published in languages other than English were omitted from this review. Once the appropriate articles were identified, the results of the studies were reviewed to arrive at conclusions as described in the section below. Guidelines for ECMO use in COVID-19 and contraindications for ECMO use in COVID-19 were also extracted from the articles that discussed ECMO use in COVID-19.

RESULTS

Use of ECMO in patients with COVID-19

A review of the year-to-date data collected by ELSO, showed 6,109 cases of reported

use of ECMO in severe COVID-19 in adult patients in North America, with an in-hospital mortality rate of 50%. Meanwhile, during the same period, 9,271 adult cases of COVID-19 on ECMO were reported globally, with an in-hospital mortality rate of 48% (ELSO, 2022). An international cohort study of 1035 patients in 213 hospitals from 36 countries with COVID-19 with ECMO support from January through May 2020 revealed an estimated in-hospital 90-day mortality of 38% (95% CI, 34.6-41.5), comparable to the non-COVID-19 patients with ARDS requiring ECMO (Barbaro et. al., 2020). This study provided a generalizable estimate of in-hospital mortality with ECMO use in COVID-19 at the beginning of the pandemic.

A systematic review and meta-analysis that evaluated the in-hospital mortality rate globally from December 2019 to January 2021 revealed a mortality rate of 37% (95% CI, 32.3-42.0) in COVID-19 patients who required V-V ECMO support versus almost 36% (95% CI, 30.7-40.7) in patients who received V-V ECMO support for non-COVID reasons. This meta-analysis included 22 observational studies involving 1896 hospitalized patients from six geographic regions in the world. Advanced age and ECMO duration were identified as risk factors for increased mortality with V-V ECMO use in COVID-19 (Ramanathan et al., 2021).

A meta-analysis and systematic review by Ling et al. (2022) that evaluated the mortality rate in patients requiring ECMO in COVID-19 over a duration of two years showed a pooled mortality of almost 49% (95% CI, 44.8-52.9). Interestingly, this meta-analysis reported higher mortality rates in studies registered during the latter half of the pandemic versus the former half.

A European observational study involving 177 centers and 1,531 patients utilizing ECMO in COVID-19 over a duration of 6 months reported an in-hospital mortality rate of 45% (Lorusso, et al., 2021). A multicenter observational study was done in five Middle Eastern countries and India with 307 hospitalized cases of refractory hypoxemia and respiratory acidosis from COVID-19 requiring ECMO support. This retrospective study collected data from over 19 centers from March 2020 to September 2020 and showed a survival to discharge home rate of 45% (Rabbie et al., 2021). This study also favored the use of ECMO in refractory hypoxemia in COVID-19. A French study involving 83 hospitalized patients who required ECMO for CARDS from March to May 2020 showed an estimated 60-day mortality rate of 31% (Schmidt et al., 2020). ECMO use in CARDS has also been associated with improved in-hospital mortality rates when compared to conventional treatment.

An observational study including more than 7,000 patients in 30 countries around the world over a duration of nearly 20 months reported that there was reduced mortality with ECMO use (26%, 95% CI, [24.5-27.5]) versus conventional treatment (33%, 95% CI, [31.8-34.6]) in selected patients with CARDS (Urner et. al.,

2022). The effectiveness of employing ECMO in CARDS remains unestablished, and the guidelines for employing ECMO in COVID-19 continue to evolve.

Guidelines for Use of ECMO in COVID-19

The ELSO has published updated guidelines for ECMO use in COVID-19 (Badulak et al., 2021). The key aspects highlighted in the guidelines include but are not limited to:

- ECMO may be employed in adults with COVID-19 and severe cardiopulmonary compromise when resources are available.
- V-V ECMO may be considered in patients with severe respiratory failure from COVID-19 with comparable outcomes to pre-pandemic V-V ECMO-supported patients.
- V-A ECMO may be considered in patients with COVID-19 with underlying severe cardiac failure, but outcome data are very limited.
- Mobile ECMO seems to be a feasible option for patients with COVID-19.
- No data exists to support increasing anticoagulation targets when compared to conventional goals for patients with COVID-19 on ECMO.
- No data exists to deviate from conventional ECMO practices.

ECMO is such an intense form of therapy that is expensive and labor-intensive. While considering the implementation of ECMO in CARDS, clinicians should consider the contraindications of ECMO that apply to the patients (despite COVID-19 status) who are being evaluated for ECMO. Identifying such contraindications prior to the referral of these patients to ECMO centers can help avoid unnecessary referrals and unnecessary use of resources.

Contraindications for ECMO

First and foremost, if a patient or the decision maker for the patient declines the use of extracorporeal support because of personal or ethical reasons, they should not be considered for ECMO. Contraindications are defined as absolute and relative contraindications as outlined in Table 1. Absolute contraindications focus on patients with several end-stage conditions, such as advanced-stage cancer; fatal intracerebral hemorrhage, cerebral herniation, or significant intracerebral hypertension; and irreversible lung parenchymal damage with no options for a lung transplant.

Relative contraindications for initiation of ECMO include advanced age (>70 years), immunocompromised states (pathologic or pharmacological), right heart failure, refusal of blood products (because of personal or religious reasons), severe coagulopathy, hematological malignancies, limited vascular access, and do not resuscitate (DNR) status. A simplified acute physiology (SAPS II) score of >/= 60, sequential organ failure assessment (SOFA) score of > 20 points, Respiratory ECMO Survival Prediction (RESP) score of </= -2 points, and a PREdiction of Survival on

ECMO Therapy (PRESET) Score of >/= 6 points are also relative contraindications for the initiation of ECMO. Being on injurious ventilator settings for refractory hypoxia for a duration of more than seven days is also a relative contraindication for the initiation of ECMO in patients with CARDS (Harnisch & Moerer, 2021). Please see Table 1 for a list of the contraindications.

Table 1.

Contraindications of ECMO Therapy

Absolute Contraindications	Relative Contraindications
• Patient/family declining ECMO • Advanced-stage cancer • Fatal cerebral hemorrhage or cerebral herniation or significant intracranial hypertension • Irreversible lung parenchymal damage with no options for transplant	• Advanced age (usually >70 years) • Immunocompromised states • Right heart failure • Hematological malignancies • Severe coagulopathy • Limited vascular access • DNR status • Simplified acute physiology (SAPS II) score of >/= 60 • Sequential organ failure assessment (SOFA) score of > 20 • Respiratory ECMO Survival Prediction (RESP) score of </=-2 • PREdiction of Survival on ECMO Therapy (PRESET) Score of >/= 6 • Being on injurious vent settings for refractory hypoxia for > 7 days

Implications for Clinical Practice

Although the effects of employing ECMO in COVID-19 patients with severe cardiopulmonary failure are not clearly established, ECMO may be considered in adults with COVID-19 and severe cardiopulmonary compromise when resources are available. Facilitating research with data submission is the key to developing optimal ECMO recommendations for COVID-19 patients. Although the duration of

V-V ECMO run in COVID-19 was longer than ECMO run in non-COVID-19 patients, the mortality rate seems to be similar in both these groups. The use of V-A ECMO in COVID-19 patients with severe cardiac failure may be considered, but limited data are available on survival benefits (Badulak et al., 2021).

While considering initiation of ECMO for COVID-19 it is important to understand that ECMO is not free of complications, and the complex pathophysiology involved in COVID-19 can make these complications even worse. Thrombosis and hemorrhage constitute the main complications associated with ECMO (Ranucci et al., 2022). COVID-19 itself is associated with an increased risk of thrombosis from underlying endothelial injury, excessive inflammation, hypercoagulability, and platelet activation (Gorog et al., 2022). Other complications associated with ECMO include infection, renal failure, vascular complications, mechanical complications, and neurological complications (Nakasato et al., 2018). Despite the availability of many risk stratification instruments to guide the initiation of ECMO, no such instruments exist to guide the withdrawal of ECMO. Suboptimal therapeutic response and adverse events are generally considered appropriate indications for withdrawal of care. This is mostly true in COVID-19 patients on ECMO, who are more prone to thrombotic and bleeding complications (Murugappan et al., 2021).

Although full vaccination against COVID-19 is very effective against the Alpha variant and moderately effective against the Gamma, Beta, and Delta variants (Zeng et al., 2022), the continuing evolution of resistant strains of COVID-19 still poses a threat to incidences of CARDS in the future. As such, prompt identification of CARDS, along with early identification and referral of potential candidates to tertiary care centers with ECMO availability, are key in the care of patients with COVID-19, who develop CARDS. At the same time, clinicians need to consider the contraindications (both absolute and relative) while considering the initiation of ECMO in patients with CARDS. The decision to refer for ECMO should be made with great care and possibly after multidisciplinary meetings seeking expert consultation. Easy accessibility and availability should not force the decision to initiate ECMO. Instead, the decision to initiate ECMO should be focused on achieving a patient-centered outcome that is feasible and meaningful (Harnisch & Moerer, 2021).

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