Graduate Medical Education Research Journal

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Volume 3 | Issue 1 Article 9

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Introduction: Veno-venous extracorporeal membrane oxygenation (VV ECMO) is an indicated treatment for severe acute respiratory distress syndrome (ARDS) refractory to conventional medical treatment. Severe ARDS is a common complication of CoVID-19 infection. Subsequently, the efficacy of VV ECMO in CoVID-19 severe ARDS patients must be investigated. ECMO is a resource-intensive treatment modality, meaning that its use must be reserved for patients with robust indications and paucity of contraindications.

Methods: We performed retrospective chart review of three patients at the University of Nebraska Medical Center that were placed on VV ECMO secondary to severe ARDS from CoVID-19 infection.

Results: All patients were male with a median age of 39 years. Two patients were of Hispanic descent, and the third was of Asian descent. No patients had underlying lung disease, and all patients had type II diabetes mellitus. Median time on mechanical ventilation prior to ECMO cannulation was six days. Median duration of ECMO treatment was 21 days with a range of 17 to 27 days. All patients were decannulated from ECMO during their hospital stay, and all patients survived to 60 days post-hospital discharge. Complications while on ECMO included GI bleeding in two patients, hematuria in one patient, necessitation of vasodilator and vasopressor support in all patients, AKI in two patients, secondary bacterial pneumonia in two patients, and blood cultures positive for gram-positive organisms in all patients. No patients suffered DVT or CVA. All patients required pRBC transfusion during ECMO treatment. Two patients were treated with remdesivir and one patient received baricitinib, a JAK-inhibitor.

Conclusion: VV ECMO is a viable treatment for patients with severe ARDS secondary to CoVID-19 infection that have failed conventional therapy. Stringent adherence to inclusion and exclusion criteria is imperative. VV ECMO combined with lung protective ventilation strategies with a focus on minimizing driving pressure can provide life-saving treatment to patients with severe ARDS secondary to CoVID-19 infection

Keywords

ECMO, VV ECMO, CoVID-19, Coronavirus, Driving Pressure, Treatment, Outcomes

VV ECMO for Treatment of Severe ARDS in COVID-19 Patients at UNMC

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https://doi.org/10.32873/unmc.dc.gmerj.3.1.008

Abstract

Veno-venous extracorporeal membrane oxygenation (VV ECMO) is an indicated treatment for severe acute respiratory distress syndrome (ARDS) refractory to conventional medical treatment. Severe ARDS is a common complication of COVID-19 infection. Subsequently, the efficacy of VV ECMO in COVID-19-related severe ARDS patients must be investigated. ECMO is a resource-intensive treatment modality, meaning that its use must be reserved for patients with robust indications and paucity of contraindications. We performed a retrospective chart review of three patients at the University of Nebraska Medical Center that were placed on VV ECMO secondary to severe ARDS from COVID-19 infection. All patients were male with a median age of 39 years. Two patients were of Hispanic descent, and the third was of Asian descent. No patients had underlying lung disease, and all patients had type II diabetes mellitus. Median time on mechanical ventilation prior to ECMO cannulation was six days. Median duration of ECMO treatment was 21 days with a range of 17 to 27 days. All patients were decannulated from ECMO during their hospital stay, and all patients survived to 60 days post-hospital discharge. Complications while on ECMO included GI bleeding in two patients, hematuria in one patient, necessitation of vasodilator and vasopressor support in all patients, AKI in two patients, secondary bacterial pneumonia in two patients, and blood cultures positive for gram-positive organisms in all patients. No patients suffered DVT or CVA. All patients required pRBC transfusion during ECMO treatment. Two patients were treated with remdesivir and one patient received baricitinib, a JAK-inhibitor. VV ECMO is a viable treatment for patients with severe ARDS secondary to COVID-19 infection that have failed conventional therapy. Stringent adherence to inclusion and exclusion criteria is imperative. VV ECMO combined with lung protective ventilation strategies with a focus on minimizing driving pressure can provide life-saving treatment to patients with severe ARDS secondary to COVID-19 infection.

Introduction

As of March 2021, there have been 124 million COVID-19 cases globally, including over 2.7 million deaths. In the U.S., 30 million COVID-19 cases have been confirmed with more than 540,000 deaths.[1] Between March 1, 2020, and August 16, 2020, the U.S. experienced 260,000 more deaths than the five-year average for that period.[2] Peak daily hospital admissions of patients with confirmed COVID-19 in the U.S. were over 18,000 in early January 2021.[3] Twenty percent of hospitalized patients in New York City required ICU-level care, with roughly 80% of ICU patients requiring mechanical ventilation.[4]

Extracorporeal membrane oxygenation (ECMO) is a viable treatment for severe acute respiratory distress syndrome (ARDS) due to various causes. Veno-venous extracorporeal membrane oxygenation (VV ECMO) is the most common modality of extracorporeal support used for severe respiratory failure not amenable to medical interventions.[5] VV ECMO is a device that replaces native lung function in situations of severe pulmonary failure, typically due to ARDS. It functions by utilizing a membrane lung to provide oxygen and remove carbon dioxide, then returning oxygenated blood back to the patient. In patients with both respiratory and cardiac failure, veno-arterial (VA) ECMO can provide surrogate pulmonary and cardiac function. At many medical institutions, including our own, VV ECMO has been used to treat patients with severe ARDS, bacterial or viral pneumonia, status asthmaticus, bronchopleural fistulas, and mediastinal masses. It also serves as a bridge to lung transplantation for individual patients and can be used as a temporizing measure in post-operative patients experiencing respiratory failure.[6,7] By facilitating lung-protective ventilation (LPV), ECMO reduces long-term lung injury by minimizing barotrauma, volutrauma, atelectrauma, and oxygen toxicity during recovery.[7] Fig. 1 below provides a depiction of the ECMO circuit.

The inclusion criteria for ECMO vary by institution. One standard measure is the Murray Lung score. Scores above 2.5-3 are commonly used to indicate the need for ECMO.[6–8] Uncompensated hypercapnia with an arterial blood gas pH <7.20 is another common indication.[6–8] A 2018 study defined severe ARDS in three ways, as described in Table 1.[9] The Extracorporeal Life Support Organization (ELSO) has provided guidelines for ECMO indications and contraindications as well as special considerations for management (Table 2). These definitions and protocols are used by many institutions worldwide when deciding if a patient is a candidate for ECMO. Common contraindications to the use of ECMO include

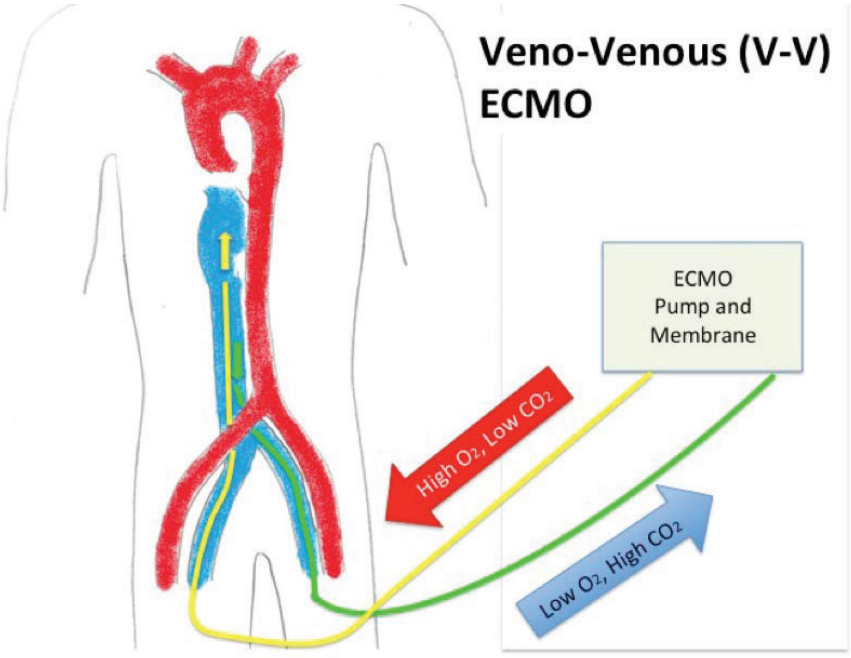

Figure 1. Diagram showing flow of blood from patient to membrane lung, and back to patient for ECMO support. Blood is drained from the patient at the level of the IVC and returned to the level of the right atrium. Image courtesy of Dan Johnson, MD. Used with permission.

end-stage pulmonary disease, multi-system organ failure, ineligibility for transplantation, morbid obesity, intracranial bleeding, contraindications to systemic anti-coagulation, recent major CVA, prolonged mechanical ventilation (usually > 7 days), and age > 65 years.[6–8]

Case

Three patients at our center have been placed on VV ECMO for severe ARDS secondary to confirmed COVID-19 infection. All patients were male with a median age of 39 years and a median BMI of 24.71 kg/m^2. Two patients were of Hispanic descent, while the third was of Asian descent. Pre-existing medical conditions included type II diabetes mellitus in all patients, one patient with hypothyroidism, and one patient with a history of pericarditis in 2018. No patients had a history of lung disease or tobacco use. Inclusion criteria at our institution are shown in Table 3 below. These criteria were developed in response to the increased mortality of COVID-19 in patients with certain risk factors including age > 65, male gender, obesity, hypertension, COPD, diabetes mellitus, malignancy, and cardiac disease.

Indications for ECMO included one patient with hypoxia (P/F ratio <100), while two patients were initiated due to combined hypoxia (P/F <150) and hypercapnia. No patients received nitric oxide or bicarbonate infusion prior to ECMO. Prior to ECMO cannulation, all patients received maximal medical therapy including neuromuscular blockade, prone positioning, inhaled epoprostenol, and maximal lung protective mechanical ventilation settings. Femoral-femoral venovenous cannulation was performed for each patient at the bedside. Ultrasound guidance was used, along with standard Seldinger technique, for venous access. Serial dilation was then performed until cannulas were placed and confirmed via ultrasonography and chest/abdomen radiographs. Fig. 2 shows a chest radiograph of proper ECMO cannula placement.

The median time on mechanical ventilation before ECMO initiation was six days. The mechanical ventilation mode utilized was pressure-regulated volume control (PRVC) for all patients prior to ECMO initiation. PRVC is the preferred ventilator mode, as it allows close monitoring of airway pressures. Lung protective strategies that emphasize low tidal volumes and low driving pressure are fundamental strategies to avoid barotrauma and volutrauma in these patients. Driving pressure is defined as plateau pressure minus PEEP. Driving pressure less than 14 cm H2O is associated with increased ARDS survival.[10,11] In fact, a New England Journal of Medicine (NEJM) article recently showed a linear relationship between changes in driving pressure and plasma concentrations of inflammatory markers like IL-6, IL-10, TNFα, and others.[12]

All patients were successfully decannulated from ECMO during their hospital stay. The median duration of ECMO treatment was 21 days with the shortest duration being 17 days and the longest being 27 days. Median length of hospital stay after decannulation was 24 days. Median length of hospitalization was 47 days, with median time in the ICU of 44 days. Survival at hospital discharge and 60 days post-hospital discharge were 100%.

Two patients experienced gastro-intestinal bleeding during treatment on ECMO, with one patient requiring partial bowel resection. One patient developed hematuria. All patients required red blood cell transfusions, with a median of 17 units during ECMO therapy. One patient also required transfusion of 3 units of platelets, 2 units of fresh frozen plasma (FFP), and 10 units of cryoprecipitate. There was no incidence of DVT or stroke. All three patients required vasodilators and vasopressors during their treatment. One

Table 1.
Respiratory and ventilator parameters that qualify for VV ECMO.

1. PaO2:FiO2 <50 mmHg for >3 hours
2. PaO2:FiO2 <80 mmHg for >6 hours
3. Arterial blood pH <7.25 with a PaCO2 >60 mmHg for >6 hours and RR of 35 bpm and plateau pressure <32 cm of H2O and FiO2 >0.8 and Tidal Volume 6 mL/kg and PEEP >10 cm of H2O

PaO2: arterial oxygen partial pressure; FiO2: fraction of inspired oxygen; PaCO2: arterial carbon dioxide partial pressure; RR: respiratory rate; PEEP: positive end-expiratory pressure

Table 2.
Indications and Contraindications to placement onto ECMO. P/F: ratio of PaO2 to FiO2.

Indications for ECMO	1. Mortality risk > 80% 2. P/F < 80 with FiO2 > 0.90 3. Murray Lung Score of 3-4
Consideration for ECMO	1. Mortality risk > 50% 2. P/F < 150 with FiO2 > 0.90 3. Murray Lung Score of 2-3
Contraindications to ECMO	1. Conditions incompatible with normal life 2. Pre-existing conditions affecting quality of life a. CNS status b. End stage malignancy c. Risk of systemic bleeding with anticoagulation 3. Age>65 4. Futility a. Patients who are too sick (ie. Immunosuppression) b. Have been on conventional therapy too long (Mechanical ventilation > 7 days)

Table 3.
Inclusion criteria used at UNMC for placement onto VV ECMO for ARDS secondary to SARS-CoV-2 disease.

1. P/F ratio of less than 100 despite aggressive mechanical ventilation including FiO2 of 1.0, PEEP greater than 16, neuromuscular blockade, +/- prone.
2. Elevated peak airway pressures (greater than 40 mmHg) and/or plateau airway pressures (greater than 30 mmHg) despite lung protective mechanical ventilation and maximal medical therapy.
3. pH of 7.2 or less with inability to correct respiratory acidosis with aggressive mechanical ventilation.
4. PaCO2 of 50 or greater despite maximal medical therapy, aggressive mechanical ventilation, and respiratory rate greater than or equal to 30 breaths per minute.
5. Mechanical ventilation performed for 3-7 days
6. Can accept patients on mechanical ventilation over 7 days on a case-by-case basis after review and agreement by all teams.

patient required inotropic agents, and one required two minutes of CPR before ROSC after a tracheostomy change. Two patients suffered acute kidney injuries, with one requiring 17 days of continuous venovenous hemodialysis. Pneumothorax was seen in two patients. Two patients developed secondary bacterial pneumonia, while all three patients had blood cultures displaying gram-positive organisms. A positive urine culture was seen in one patient. Fig. 3 depicts these complications.

Two patients were treated with remdesivir and one received barcitinib, a JAK-inhibitor. Prone position was not used while on ECMO. One patient was discharged home, and two were discharged to long term acute care. Sixty-day survival after hospital discharge was 100% in our patient population. All patients required tracheostomies during their hospitalization. Of note, one patient was able to be decannulated from their tracheostomy prior to hospital discharge.

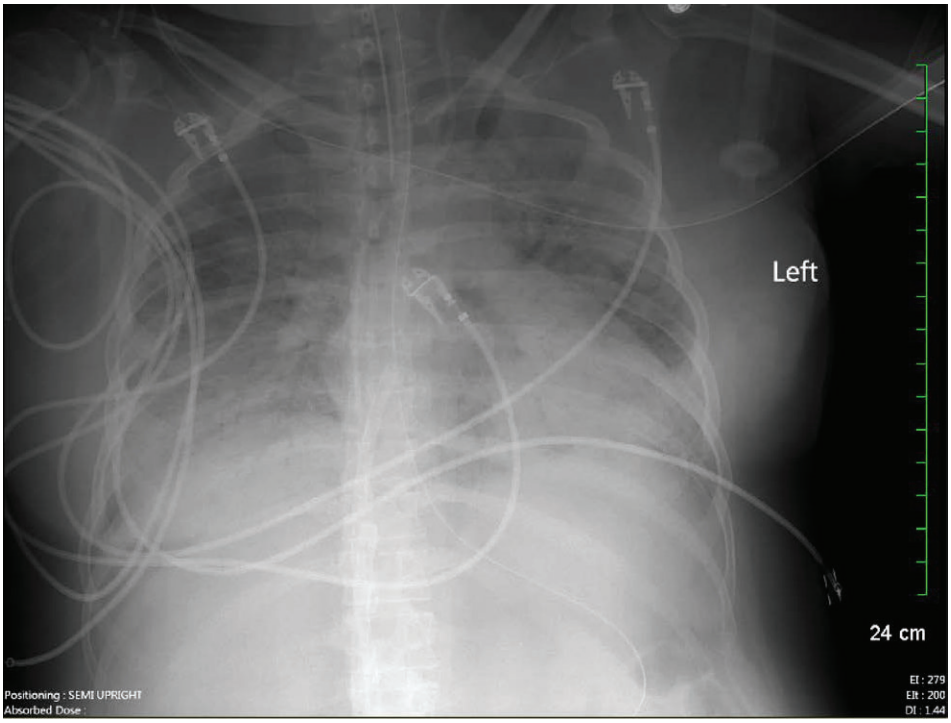

Figure 2. Chest x-ray showing diffuse pulmonary opacities consistent with SARS-CoV-2 infection.

Discussion

All of our patients (100%) in this case series survived to ICU discharge, hospital discharge, and 60 days post-hospital discharge. One study with a larger patient population with any ARDS etiology displayed survival to ECMO ICU discharge of 74%.[6] Median duration of ECMO in the said study was 191 hours, while ours was 21 days (504 hours).[6] Our patients spent a median time of 47 days in the hospital, compared to 16 days in the England study.[5,6] Incidence of pneumothorax in our patients was 67% compared to an incidence of 10.4% at other centers.[6] Sixty seven of our patients developed culture-proven bacterial pneumonia, and 100% developed culture-proven bloodstream infections. Culture proven infection occurred in only 15% of patients in the England study.[6] A *NEJM* study compared severe ARDS patients (defined in the introduction) placed on ECMO to a control group that only received standard treatment. Sixty-day survival in the ECMO group was 65% compared to 54% in the control group.[9] The ECMO group had a higher incidence of bleeding events requiring transfusion and severe thrombocytopenia, but had fewer ischemic stroke cases.[9] All patients in our study required RBC transfusion at some point during their care. Similarly, no patients suffered from stroke or DVT during their treatment. All our patients had underlying poorly controlled type II diabetes mellitus.

VV ECMO provides relief to the dysfunctional pulmonary system in patients with severe ARDS, allowing time for lung recovery. Lung recovery is most effectively facilitated through LPV strategies that minimize barotrauma and volutrauma. In fact, minimization of driving pressure is associated with increased survival and reduced inflammatory marker levels in ARDS

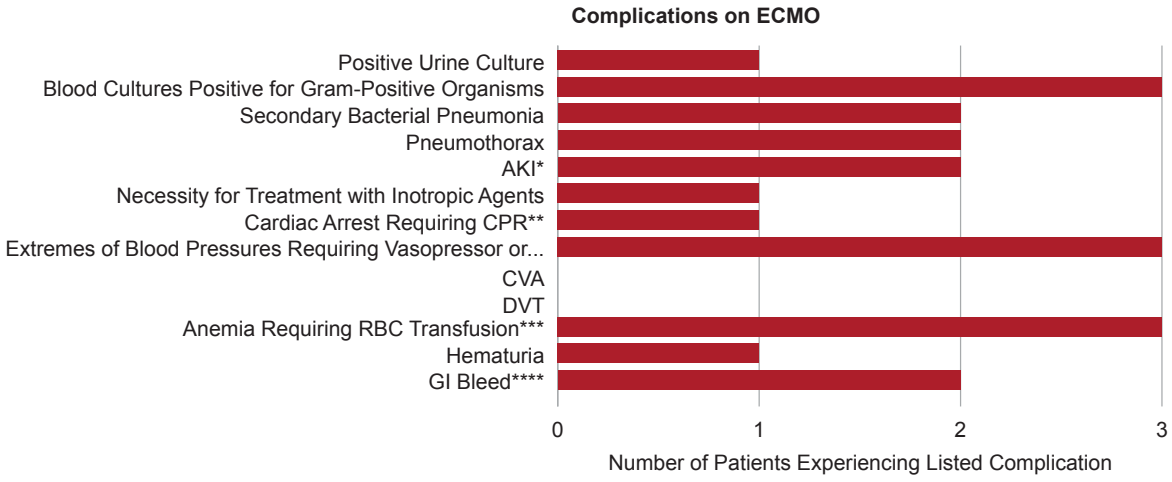

Figure 3. List and number of patients suffering from complications related to or a consequence of ECMO therapy.

patients.[10-12] At the University of Nebraska Medical Center (UNMC), our standardized LPV protocol includes tidal volumes of 4-6 mL/kg of predicted body weight, pressure-regulated volume control (PRVC) ventilator settings, PEEP of 8-16 cm H_2O, RR <10 bpm, plateau pressure < 30 mmHg, and driving pressure < 15 mmHg if able. These protocols not only give our patients the greatest chance of survival, but also help to reduce long-term complications caused by high airway pressures.

Conclusion

VV ECMO, when combined with LPV, is a powerful, but resource-consuming treatment modality for patients suffering from severe ARDS. A robust study in England reported 74% of patients requiring VV ECMO for respiratory failure secondary to numerous causes survived to ICU discharge.[6] Another substantial study showed 90-day in-hospital mortality after initiation of VV ECMO in patients suffering severe ARDS secondary to COVID-19 infection was 38%, similar to the mortality rates reported in non-COVID-19 cases of severe ARDS.[5] Sixty day survival in our patient cohort was 100%, displaying the validity of treating COVID-19-induced severe ARDS with VV ECMO and LPV.

An important theme in the study of treating ARDS with VV ECMO is the careful selection of patients and use of strict mechanical ventilation strategies to minimize further lung damage. ECMO is a resource-intensive treatment that serves only as a bridge to recovery or transplant. Therefore, careful selection of patients with high likelihood of recovery is necessary. Contraindications for the practical and effective use of this treatment modality include, but are not limited to, end organ failure, minimal hope of recovery after decannulation, age >65, advanced cancer diagnosis, morbid obesity, and recent intracranial pathology. This careful utilization of resources is essential to the success of the treatment and patient outcomes.

ECMO is a viable treatment for COVID-19-induced severe ARDS. However, especially in pandemic times and the resulting limitation in resources, increased selectivity and strict adherence to protocols are necessary to ensure the best patient outcomes. In our experience, COVID-19-induced severe ARDS results in longer duration of ECMO, a longer duration of ICU care, and more extended hospitalization than other causes of severe ARDS. ■

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