Extracorporeal membrane oxygenation with right ventricular support in COVID-19 patients with severe acute respiratory distress syndrome

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Video clip is available online.

CENTRAL MESSAGE

Single access, dual-stage veno-venous ECMO with right ventricular support is safe and effective in COVID-19 patients with severe acute respiratory distress syndrome in whom mechanical ventilatory support is failing.

Rare cases of COVID-19 infection can lead to life-threatening respiratory failure.[1] Despite attempts to control the disease with social distancing and mass vaccination, 2% of patients continue to succumb to lung injury related to infection with this virus.[2] Mechanical ventilatory support is the primary intervention for patients with worsening respiratory failure progressing to acute respiratory distress syndrome.[3,4] Barotrauma, prolonged sedation, and nosocomial pneumonia in patients who require mechanical support further lead to secondary complications and potentially limit recovery.[5]

Veno-venous extracorporeal membrane oxygenation (ECMO) has been used in severe cases of respiratory failure.[6-8] The international Extracorporeal Life Support Organization reported a 51% survival in patients with COVID-19 respiratory failure who were supported with ECMO.[9] The largest US multicenter study reported a survival of 42%.[10] Several cannulation strategies can be applied, and no randomized clinical trial has evaluated the superiority of one technique over another.

Throughout the pandemic our practice has applied veno-venous ECMO with right ventricular support using a dual-stage right atrium to pulmonary artery cannula, the Protek-Duo (CardiacAssist, Inc), for COVID-19 infected patients with respiratory failure in whom conventional mechanical ventilatory support has failed. The rationale for adopting this system was on the basis of inadequate support observed in patients supported with 2 venous cannulas. Recirculation using 2 venous cannulas for support and difficulty mobilizing the patient provided the impetus for change.

Conversion to a single access site with right atrial to pulmonary artery catheter provided several advantages: stable platform with rare catheter malposition, adequate flows, and decreased recirculation of drainage blood. Ambulation with this system was simplified. Even with limited patient access with patients in quarantine and during subsequent prolonged support with ambulation catheter malposition was uncommon.

Moreover, pulmonary artery pressure measurements were conducted during catheter implantation, and showed severe pulmonary hypertension in all patients. Acute cor pulmonale in COVID-19 patients carries significantly higher mortality,[11,12] and obesity and acute respiratory distress syndrome are independent risk factors for right ventricular failure.[13,14] As such, the Protek-Duo was chosen over other single access dual lumen catheters because of the additional potential for right ventricular support, with flow directly into the pulmonary circulation. Although the limitation of this cannula has not been evaluated, the

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durability of this system has been observed in a patient maintained on support for 10 months using a single cannula.

Over the past year and a half, 150 patients were supported with ECMO using the single access, dual-stage right atrium to pulmonary artery cannula. Early results of our first 40 patients were published in *JAMA Surgery*.[15,16] Survival to discharge was 82.5%.[16] As the care of patients with COVID-19 infection requiring ECMO has evolved, we describe our approach, patient selection, institutional requirements, cannulation strategy, management, and the results of our experience. All patients were treated and studied at Advocate Christ Medical Center (AHC-7426-C5000376) and Rush University Medical Center (ORA-20040401) from March 17, 2020, and onward. Waiver of the need for consent was obtained. The data were deidentified during analysis and publication to protect patient privacy.

Of the 136 patients who have completed their hospital course, 75% were extubated from the ventilator, and 67% decannulated from ECMO and discharged alive. Only 3% required long-term rehabilitation, and 24% needed supplemental oxygen at discharge. The average time for mechanical ventilation was 23.5 ± 5.4 days, and ECMO was 48.4 ± 4.9 days. The average age was 46.9 (SEM, ± 1.1) years; 71% were men and 52% were Hispanic. The average body mass index (BMI) was 34.3 ± 0.6, with obesity noted in 68% of the patients. More than 80% were prone, chemically paralyzed, and receiving vasopressors before ECMO initiation.

Major complications such as stroke, as well as acute kidney or liver injuries, were limited. Tracheostomy was performed in 13% of patients. Mortality was 95% in this subgroup.

PATIENT SELECTION

Criteria for ECMO were based on Extracorporeal Life Support Organization principles. Patients supported were younger than 70 years old with single organ dysfunction and suffering from severe hypoxia or hypercarbia despite maximum ventilatory support similar to the stringent criteria described by the ECMO to rescue acute lung injury in severe ARDS trial group.[7] Although most patients supported were obese, absolute BMI weighed into the decision to offer ECMO support. BMI <50 was preferred. Extreme obesity provides additional challenges, and these include difficulty ambulating patients and assuring adequate ECMO flows. The limitations of institutional resources such as critical care hospital beds and nursing staff were additional factors in our decision-making. Some of the absolute contraindications to ECMO placement were outlined in our previous publication.[15] Briefly, they include patients who have suffered a cardiac arrest without return of spontaneous circulation, those with severe acidosis or significantly elevated lactate levels, patients with multi-system organ failure, those with projected life expectancy <5 years before COVID-19 infection, as well as patients with known severe preexisting chronic, life-threatening conditions. Patients on the mechanical ventilator for >2 weeks were not considered for support.

INSTITUTIONAL REQUIREMENTS

Successful application of ECMO requires a dedicated, experienced team with coordinated care of physicians, allied health professionals, perfusionists, respiratory, physical, occupational, and speech therapists, pharmacists, and nutritionists. Critical care nursing is paramount. Cardiothoracic surgeons are core team members whose expertise provides leadership and guidance in the management of these patients. Institutional limitations due to physical space and staffed beds dictate capacity. Focused units provide consistent adherence to principles of ECMO support.[17] Adequate supplies of pumps, oxygenators, and cannulas are required. A variety of support systems are now available for which no direct comparisons have been published. Centrifugal pumps, including Abbott Centrimag and LivaNova Revolution with Maquet Quadrox or occasionally Medtronic MC3 Nautilus oxygenators, have been used in all of our patients. Recovery is slow, often requiring months of in-hospital care.

ECMO PHYSIOLOGY

Veno-venous ECMO works parallel to the native circulation, so there will always be a mixing of oxygenated ECMO blood with desaturated native venous blood. Therefore, no veno-venous support system will thoroughly oxygenate all blood entering the arterial system. If desaturated native venous flow (ie, the cardiac output) increases while the ECMO flow is constant, the arterial saturation will decrease.[17] Extreme oxygen extraction also leads to a reduction in native venous saturation, which decreases arterial saturation at constant ECMO flow. As such, optimizing oxygen delivery and evaluating oxygen consumption are important principles of ECMO management. The goal is to maintain oxygen delivery at least 3 times oxygen consumption.[17] This requires a calculation of the arterial blood oxygen content, which on the basis of the partial pressure of oxygen, oxygen saturation, and hemoglobin levels. Despite single access, veno-venous ECMO, patients with extreme BMI, high cardiac output, and significant oxygen extraction might still be hypoxemic. Assessment of arterial lactate in these patients is also critical to the determination of adequate support. As long as oxygen delivery is >3 times oxygen consumption, aerobic metabolism is assured, and lactate will typically be within normal limits.

CANNULATION

Although a variety of cannulation strategies are feasible, a single access, dual-stage right atrium to pulmonary artery cannula with access through the internal jugular vein was primarily used in most of our patients. Properly secured cannula placement is critical (Figure 1). Placement requires fluoroscopy, and is best performed in an operative or hybrid suite where imaging is optimal; however, bedside insertion with portable imaging has been required for patients unable to tolerate any movement. Access most commonly is performed through the right internal jugular vein, although left internal jugular or subclavian vein approaches are equally successful. A balloon-tipped catheter is floated into the pulmonary artery and exchanged over a stiff wire. The access site is dilated, and the catheter is advanced to the main pulmonary artery. Not uncommonly, the distal tip of the catheter extends to the left or right main pulmonary artery because the length of the catheter as the inflow is best positioned to the right atrium.

Small patients are not appropriate for cannulation with the Protek-Duo because of the length of the catheter. Patients with estimated distance from the right atrium to pulmonary artery of <17 centimeters or restricted vascular access unable to accommodate a 29-French cannula are supported with alternative strategies.

Two venous cannulas without right ventricular support are the initial strategy in pediatric patients who have required ECMO support. Alternative approaches are applied for rare patients who require greater flow or pediatric patients who require ventricular support. Direct cannulation of the pulmonary artery or aorta is performed through a sternotomy. An 8- or 10-mm vascular graft is sewn to the main pulmonary artery or ascending aorta. These grafts are tunneled subcutaneously and connected to the outflow circuit. Percutaneous cannulation of the right atrium provides inflow with conversion to veno-arterial or veno-venous ECMO. Decannulation is performed with ligation of the graft and by burying of the residual stump subcutaneously without reoperative sternotomy.

Rapidly declining patients who are intolerant of transfer to the operating room are initially supported with femoral-femoral or internal jugular-femoral cannulation. With ongoing support, most of these patients are converted to the Protek-Duo. The rationale for conversion is primarily to simplify access, avoid recirculation, maintain efficient gas exchange, and provide long-term catheter stability without malposition.

Right ventricular failure is a devastating consequence in many patients with severe COVID-19 respiratory failure.[11,12] Elevated central venous and right ventricular pressures as well as significant pulmonary hypertension at the time of ECMO initiation were routinely noted. As such, supporting the right heart under these circumstances has potential benefits. We also routinely use pulmonary vasodilators such as inhaled nitric oxide.

MANAGEMENT

Awake ECMO

Initial management involves discontinuation of paralytics and minimizing ventilatory barotrauma by reducing the plateau pressures to <20 mm Hg. The goal is to extubate all patients after cannulation. Extubating patients during ECMO avoids barotrauma related to mechanical ventilation and avoids nosocomial pneumonia. Discontinuing paralytics and weaning sedatives facilitate mobilization and are associated with improved outcomes. Significant challenges are encountered when attempting to wean sedation. Agitation and increased work of breathing increase oxygen consumption and CO_2 production.

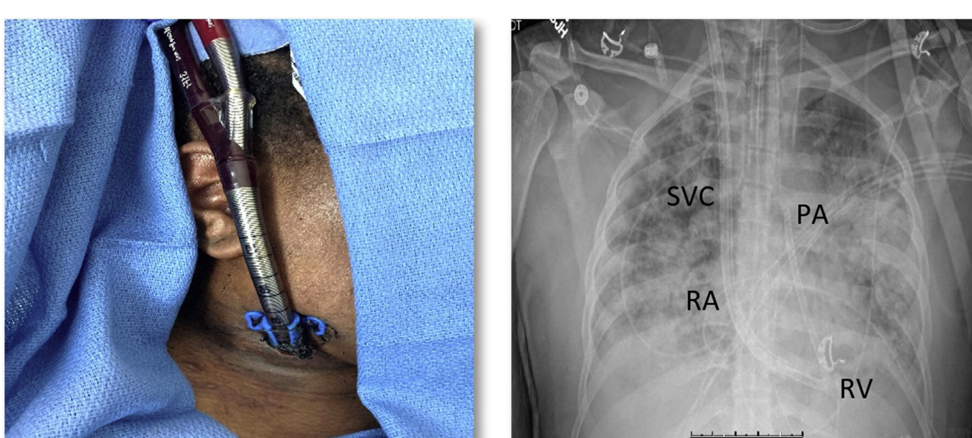

FIGURE 1. Cannulation of a COVID-19 patient undergoing extracorporeal membrane oxygenation (*ECMO*). Cannula insertion site is shown in the neck region with inflow and outflow lines attached (left). Chest radiograph shows cannula coursing through the internal jugular vein passing the right heart into the pulmonary artery (right). *SVC*, Superior vena cava; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle.

Therefore, ECMO blood flow and sweep gas flow should be increased during weaning from sedation. The rapidly rising partial pressure of CO_2 is the primary cause of agitation and dyspnea. Assessment of metabolism by measuring lactic acid is an important determinant of adequate support. Not uncommonly, patients will have transient periods of relative hypoxemia with decreased oxygen saturations during weaning trials. Getting to an awake status, and treating hypoxemia and hypercarbia cannot be managed by inexperienced caregivers by increasing ventilatory support. Relative hypoxemia must be tolerated when there is no evidence of end-organ malperfusion. Blood transfusion is required to increase oxygen content and improve delivery. Experience has shown that titrating sweep with increased CO_2 removal during episodes of symptomatic increased work of breathing has decreased the air hunger patients manifest and facilitated the ability to get patients off the ventilator.

FIGURE 2. Rehabilitation of COVID-19 patients receiving extracorporeal membrane oxygenation (*ECMO*). COVID-19 patients supported on ECMO while extubated are able to perform various activities.

Medications

Most patients will require polypharmacy while weaning, including narcotics, anxiolytics, and antipsychotics. No single combination of drugs can be applied to all patients because clinical response varies and individual tailoring of sedation is required. Patients with prolonged pre-ECMO mechanical ventilatory support with high-dose sedatives require longer weaning periods; several weeks might be required.

Anticoagulation with direct thrombin inhibitors was initiated with titration of prothrombin time between 50 and 70 seconds. Hypercoagulability is also detrimental to the ECMO circuit because clots can hamper flow and damage the oxygenator.[18] Choice of anticoagulation was initiated because of early heparin resistance and avoidance of heparin-associated antibodies.

Extubation Criteria

Extubation requires an awake, cooperative patient able to follow simple commands with stable hemodynamics without maximal flow or sweep. Arterial saturation >70% with normal lactic acid was targeted. Transfusion might be required to maintain normal oxygen content and prevent the elevation of lactic acid.

Tracheostomy is not favorable in this group of patients. Our goal is to remove the endotracheal tube, limit airway instrumentation, and provide lung recruitment over time with incentive spirometry and physical activity. With patients off ventilator support, sedatives are minimized, physical therapy is maximized, and most patients will rehabilitate on ECMO.

Rehabilitation

Rehabilitation is initiated on ECMO. Once extubated, aggressive physical, occupational, and speech therapy with nutritional supplementations are the mainstays of treatment (Figure 2). Ambulation on ECMO is critical for clinical improvement (Video 1). Not uncommonly, patients have complete opacification of lung fields that do not improve until they ambulate. After patients demonstrate increased activity and subsequent radiographic improvement, ECMO support is gradually weaned. With patients ambulating on ECMO, long-term care is uncommon after lung recovery and discontinuation of ECMO support.

VIDEO 1. Ambulating while receiving ECMO. Forty-four-year-old gentleman with COVID-19 was supported on ECMO for 143 days. The video was taken on the day of decannulation. He spent a week in short-term rehabilitation before being discharged home without supplemental oxygen. Video available at: https://www.jtcvs.org/article/S2666-2736(21)00414-9/fulltext.

Complications

Bleeding and clotting complications are observed in this cohort of patients. Patients with COVID-19 are predisposed to thrombosis, developing deep vein thrombosis, pulmonary embolus, and stroke.[19-21] Bleeding is often associated with a consumptive coagulopathy that might resolve with ECMO circuit exchange and often requires transfusion therapy. Bleeding complications delay extubation and require cessation of anticoagulation. Nasal bleeding frequently requires packing and embolization if refractory to local measures.

The outflow of the Protek-Duo limits flows in the cannula because of its small size and length with resultant resistance. Attempting to flow >4.5 L/min has been associated with hemolysis. Rare cases of cannula fracture over time have also been observed with subsequent hemolysis.

Oxygenator failure is unpredictable and therefore requires ongoing evaluation. An increase in lactate dehydrogenase levels, worsening post-oxygenator blood gases, increasing pre- and post-oxygenator pressure differentials,

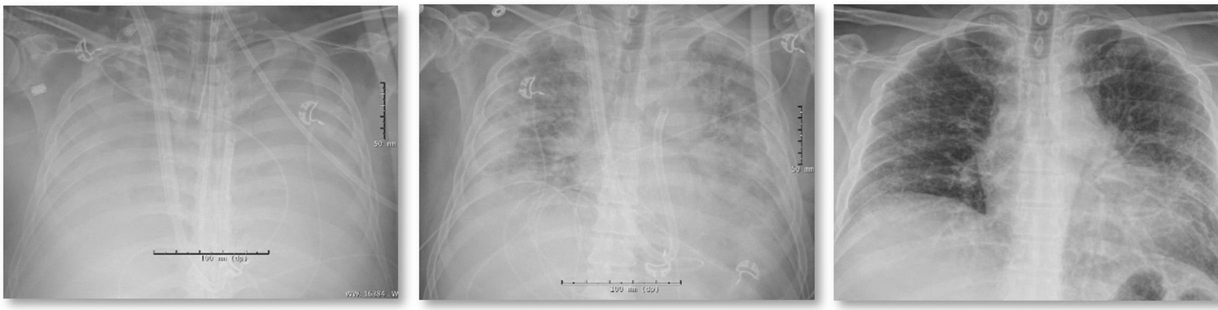

FIGURE 3. Chest radiographs of COVID-19 patients at various stages of extracorporeal membrane oxygenation (*ECMO*) support. Typical chest radiographs of a patient at different phases of treatment with significant improvement noted from complete airspace opacification to return to baseline.

and flow limitations are indicators of failure. Despite anticoagulation, oxygenators sometimes fail within days. However, oxygenators also have functioned adequately for months in the absence of anticoagulation.

Overt sepsis from bacteremia or fungemia with renal failure is associated with a poor prognosis. As such, limiting the number and duration of intravenous lines is critically important.

CONCLUSIONS

ECMO in COVID-19 patients has led to promising outcomes. Using single access, dual-stage veno-venous cannula with right ventricular support provides a stable support platform to facilitate ECMO. Alternative cannulation strategies might be required to achieve successful outcomes. Liberating the patient from sedation and mechanical ventilation, early extubation, and emphasis on physical and respiratory rehabilitation on ECMO are critical components of our treatment protocol. With this approach, patients with the most severely affected lungs with complete opacification on their chest radiographs were able to make a meaningful recovery (Figure 3), with most being discharged home alive and only a small percentage requiring long-term rehabilitation indicative of a return to a good quality of life. Recovery requires patience with prolonged hospitalization. Morbidity is significant with infectious and bleeding complications. We firmly believe in the dictum of the father of medicine, Hippocrates, "walking with ECMO is man's best medicine."

Conflict of Interest Statement

A.J.T. has served as a consultant with Abbott Laboratories, Medtronic, and Livanova outside of the submitted work. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: ECMO, COVID-19, ARDS, right ventricular support, extubation on ECMO, patient mobilization