Veno-venous Extracorporeal Membrane Oxygenation for Respiratory Failure in COVID-19 Patients

Early Experience From a Major Academic Medical Center in North America

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Summary and Background Data: VV ECMO can be utilized as an advanced therapy in select patients with COVID-19 respiratory failure refractory to traditional critical care management and optimal mechanical ventilation. Anticipating a need for such therapies during the pandemic, our center created a targeted protocol for ECMO therapy in COVID-19 patients that allows us to provide this life-saving therapy to our sickest patients without overburdening already stretched resources or excessively exposing healthcare staff to infection risk.

Methods: As a major regional referral program, we used the framework of our well-established ECMO service-line to outline specific team structures, modified patient eligibility criteria, cannulation strategies, and management protocols for the COVID-19 ECMO program.

Results: During the first month of the COVID-19 outbreak in Massachusetts, 6 patients were placed on VV ECMO for refractory hypoxemic respiratory failure. The median (interquartile range) age was 47 years (43–53) with most patients being male (83%) and obese (67%). All cannulations were performed at the bedside in the intensive care unit in patients who had undergone a trial of rescue therapies for acute respiratory distress syndrome including lung protective ventilation, paralysis, prone positioning, and inhaled nitric oxide. At the time of this report, 83% (5/6) of the patients are still alive with 1 death on ECMO, attributed to hemorrhagic stroke. 67% of patients (4/6) have been successfully decannulated, including 2 that have been successfully extubated and one who was discharged from the hospital. The median duration of VV ECMO therapy for patients who have been decannulated is 12 days (4–18 days).

Conclusions: This is 1 the first case series describing VV ECMO outcomes in COVID-19 patients. Our initial data suggest that VV ECMO can be successfully utilized in appropriately selected COVID-19 patients with advanced respiratory failure.

Keywords: ARDS, COVID-19, extracorporeal membrane oxygenation, VV-ECMO

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The 2019 coronavirus disease (COVID-19) has demonstrated a wide range of patient presentations, ranging from asymptomatic viral colonization to acute respiratory distress syndrome (ARDS) requiring intubation and advanced mechanical ventilatory strategies. In cases where respiratory failure is extreme enough to preclude adequate gas exchange despite patient optimization and optimal mechanical ventilation, veno-venous extracorporeal membrane oxygenation (VV ECMO) may serve as an additional supportive therapy in our limited arsenal against COVID-19. This role is one that ECMO has filled in the treatment of other severe viral respiratory infections such as H1N1 influenza [1,2] and current guidelines from the Society of Critical Care Medicine support its application in COVID-19.[3,4] Although not a focus of this report, a small fraction of patients has presented with COVID-19 related circulatory collapse requiring veno-arterial ECMO.

There has been significant geographical variation in the use of VV ECMO for COVID-19. Over fifty ECMO cases have been reported in Japan and South Korea compared to much smaller cohorts in China and Italy.[5–7] These discrepancies in ECMO usage are likely to be driven by differences in existing ECMO capacity and infrastructure, and variations in burden of disease and patient selection criteria across medical centers. We describe here the early experience with VV ECMO for management of COVID-19 patients at the Massachusetts General Hospital, a major regional ECMO center in North America.

ELIGIBILITY CRITERIA FOR VV-ECMO

Postmortem biopsies suggest that the pathogenesis of COVID-19 respiratory failure fits within the ARDS spectrum. Diffuse alveolar damage with flooding of alveoli and the formation of hyaline

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membranes result in decreased lung compliance and hypoxemia, which can be severe.[8] During the early days of COVID-19 in Massachusetts, our center formed a COVID-19 pandemic ECMO team consisting of cardiac and medical intensivists, pulmonologists, and cardiac surgeons that created local indications for VV ECMO in this unprecedented medical situation. A consensus was reached to offer VV ECMO to patients with severe impairment of oxygenation (P:F ratio cutoff ~80–100) with respiratory instability, characterized by either periods of prolonged desaturations or elevated airway pressures despite ventilator optimization. ECMO would not be considered until it was clear that safe ventilation was not possible despite optimization of ventilator parameters by the primary medical intensive care unit (ICU) team and attempted prone positioning. Approval was required from the ECMO team and medical ICU leadership, who had access to real time health system resource utilization statistics.

Several absolute contraindications to ECMO cannulation in COVID-19 patients were identified including age >60 years, multisystem organ failure, active malignancy, pre-existing chronic cardiac, pulmonary (not including asthma) or hepatic disease, unknown or guarded neurologic status, and severe neutropenia (Absolute Neutrophil Count <1000/mm^3). Body mass index (BMI) >35 kg/m^2 was stipulated as a relative contraindication given concerns about technical feasibility and achieving adequate VV ECMO flow rates in the setting of severe obesity. Further, this contraindication was intended to decrease the need for multiple re-interventions for flow issues caused by body habitus that would pose a risk of significant viral exposure for providers. Other relative contraindications included active bleeding, chronic renal dysfunction, immune suppression, and concurrent infection with multi-drug resistant organisms.

These criteria differed from our standard non-COVID ECMO criteria in a few meaningful ways including requirements for more severe respiratory failure (usual P:F ratio threshold <120–150) and more stringent age and BMI limitations (usual limits of 70 years and 40 kg/m^2, respectively). Currently, we are not using VV ECMO as a bridge to transplantation in COVID-19 patients. These modifications were made in the context of known patterns of mortality and the potential for resource constraints during the COVID-19 pandemic. Notwithstanding, final criteria correlated well with guidelines released by the extracorporeal life support organization for ECMO use during the COVID-19 pandemic.[5]

CANNULATION STRATEGY

General Considerations

Our cannulation strategy was designed to maximize efficiency to conserve limited personal protective equipment (PPE), protect healthcare staff from exposure, and minimize patients' time spent in hypoxia. Given that emergency procedures inherently carry a higher risk of error and consequent exposure to COVID-19 for the cannulating team, we make an effort to screen ICU patients who may need vascular access for ECMO. 4 Fr right internal jugular and femoral vein sheaths are placed early (in the setting of impending pronation) to bypass the critical step of obtaining vascular access should ECMO become necessary.

Our cannulation policy provides specific guidance limiting the number of healthcare workers in the room at the time of the cannulation procedures to 1–2 ICU nurses, 2 respiratory therapists, 2 operating room staff members, and 1–2 physicians. Additional staff members wait on standby outside the patient's room, ready to assist with clinical needs that may arise. Importantly, all potential members of the ECMO team received online and in-person training on the appropriate use of PPE.

Procedural Considerations and Cannula Selection

VV ECMO cannulation is performed at the bedside in the ICU using predominantly femoral and right internal jugular cannulas. The preference for cannulation in the ICU as opposed to the operating room limits provider exposure and risk of circuit mishap related to patient transport. Image guidance with transthoracic echocardiography is routinely used to augment surface anatomy-based estimations of appropriate cannula positioning. Avoiding transesophageal echocardiography is especially prudent during the COVID-19 pandemic as this is considered by some to be an aerosolizing procedure. Similarly, the strategy of using 1 femoral vein and 1 internal jugular vein cannula obviates the need for fluoroscopy to confirm cannula positioning. Fluoroscopy and transesophageal echocardiography were routinely used at our center during VV-ECMO cannulations before COVID-19 when a single cannula internal jugular vein strategy was employed (Dual Lumen catheter). Additionally, these cannulations were most commonly performed in the operating room. Our COVID-19 protocol considers dual lumen catheters in the internal jugular vein a very distant second option, to be employed only when both femoral veins are unusable.

We consider bifemoral (fem-fem) cannulation the least favorable strategy in these patients for a few reasons. First, most COVID-19 patients in severe hypoxic respiratory failure have presented with high cardiac output and almost nonfunctioning lungs. This poses a higher risk of recirculation with a bifemoral configuration (reinfusion of oxygenated blood from the ECMO pump/oxygenator into the drainage cannula without passing through the systemic circulation) that arises due to the proximity of cannulas in this configuration. Second, there are theoretical concerns about restriction in maximal flow rates with the bifemoral configuration. We have therefore reserved this approach for situations where both the subclavian and internal jugular veins are not available (eg, in the setting of pre-existing venous thrombosis).

Cannula Sizes

In advanced COVID-19 related respiratory distress requiring VV ECMO, the contribution of the lungs to systemic oxygenation is truly negligible, thus necessitating very high flow rates that can only be reliably supplied by large cannulas. Generally, VV ECMO flow rates should be titrated to ~60–80 mL/kg/min to completely support systemic oxygenation.[9] As many of the patients we encounter are overweight or obese, this translates to flow requirements of greater than 5 L/min in many cases (Table 2). Thus we have chosen to place 19–21 Fr cannulas in the right internal jugular vein and a 25 Fr cannula in the femoral vein. Larger (21 Fr) cannulas are used for the internal jugular vein in patients with a body surface area >2.2m^2.

MANAGEMENT ON VV ECMO

The primary function of VV ECMO is to support the patient while the lungs recover from the Severe acute respiratory syndrome–Coronavirus 2 (SARS-CoV2) mediated cellular cytotoxic insult, permitting the use of ultra-protective lung ventilatory strategies. Therapeutic anticoagulation is standard practice in the absence of bleeding concerns. Patients are typically kept sedated during the duration of the ECMO run with routine monitoring of neurological status. Based on early reports, we anticipated longer than usual runs on VV ECMO for COVID-19 populations (initial reports of 22–47 days of VV ECMO for COVID-19 patients).[6] Our standard local weaning protocols are applied, driven by improvements in gas exchange (based on routine arterial blood gas monitoring), tidal volume, and lung compliance as the lung injury resolves.

Attempts at decannulation are preceded by a cap trial (period of 0 L/min ECMO sweep gas flow). When it is certain that support

TABLE 1. Baseline Characteristics

	COVID-19 + VV ECMO (n = 6)
Demographics	
Age (median, IQR)	47 (43–53)
Female (n, %)	1 (17)
Body mass index, kg/m^2 (median, IQR)	31.2 (31–35)
Body surface area, m^2 (median, IQR)	2.00 (2–2)
Past medical history	
Former or active smoker (n, %)	2 (33)
Asthma (n, %)	1 (17)
Diabetes mellitus (n, %)	4 (67)
Coronary artery disease (n, %)	0 (0)
Hypertension (n, %)	3 (50)
Chronic obstructive pulmonary disease (n, %)	0 (0)
History of malignancy (n, %)	0 (0)
Chronic kidney disease (n, %)	1 (17)
Obesity (n, %)	4 (67)
Hyperlipidemia (n, %)	2 (33)
ACE inhibitor use (n, %)	2 (33)
Presentation history	
Confirmed COVID-19 RT-PCR (n, %)	6 (100)
Concurrent influenza or RSV detected (n, %)	0 (0)
Time from admission to intubation, days (median, IQR)	0 (0–0.75)
Time from admission to ECMO cannulation, days (median, IQR)	5.5 (3.5–6.75)
Patients transferred from outside hospital before ECMO cannulation (n, %)	4 (67)
Patients cannulated with ECMO at outside hospital (n, %)	0 (0)
Prone positioning before ECMO (n, %)	6 (100)
Paralyzed before ECMO (n, %)	6 (100)
Inhaled nitric oxide before ECMO (n, %)	6 (100)
Medications used during hospital course	
Hydroxychloroquine (n, %)	6 (100)
Remdesivir trial (n, %)	2 (33)
Tocilizumab (n, %)	3 (50)
Lopinavir/ritonavir (n, %)	1 (17)
Azithromycin (n, %)	3 (50)
Labs at time of ECMO cannulation	
Lactate dehydrogenase (median, IQR)	419 (386–543)
D-dimer (median, IQR)	2106 (1550–3310)
INR (median, IQR)	1.2 (1.1–1.4)
Creatinine (median, IQR)	1.8 (0.9–2.7)
P:F ratio (median, IQR)	95 (84–100)

COVID-19 indicates coronavirus disease 2019; IQR, interquartile range; RSV, respiratory syncytial virus; VV ECMO, veno-venous extracorporeal membrane oxygenation.

will no longer be needed, anticoagulation is discontinued and the ECMO system is decannulated at the bedside with hemostasis obtained via reinforced pressurizing sutures and manual pressure. Following decannulation, patients are progressed steadily toward liberation from the ventilator. A comprehensive pulmonary rehabilitation program is instituted post-extubation and continues after discharge from the hospital.

PATIENT CHARACTERISTICS

As of April 16, 2020 6 COVID-19 patients with respiratory failure have been treated with VV ECMO at our institution. All patients had confirmed positive COVID-19 RT-PCR results before time of cannulation. The median age of the cohort was 47 years old [interquartile range (IQR) 43–53] and 83% (5/6) of patients were male. Median BMI was 31.2 kg/m^2 (IQR 31–35) and median body surface area was 2.00 m^2 (IQR 2–2). The most common co-morbidities were diabetes mellitus (4/6, 67%) and obesity (4/6, 67%). No patients had co-occurring influenza or respiratory syncytial virus.

Patients were intubated early in their admission and the median time from admission to ECMO cannulation was 5.5 days (IQR 3.5–6.75). Sixty-seven percent (4/6) of patients were transferred to us from outside institutions; however, all 6 patients were cannulated with ECMO at our institution. All patients had undergone a trial of paralytic, prone positioning, and inhaled nitric oxide before ECMO cannulation. All patients had received a 5-day course of hydroxychloroquine during their hospitalization (Table 1).

All patients were cannulated at the bedside in the ICU with 19 or 21 Fr cannulas in the right internal jugular vein and 25 Fr cannulas in the right femoral vein. Patients have required high flow rates (range 4.1–6.0 L/min) and displayed high plateau pressures (range 21–30 cm H_20) during the ECMO run (Table 2).

ECMO COMPLICATIONS AND OUTCOMES

Thus far, 67% (4/6) of patients have successfully survived ECMO decannulation. Two of these patients have also been extubated, and 1 was discharged from the hospital after 2 negative COVID-19 RT-PCR tests. The median duration on ECMO for those who survived to decannulation was 12 days (4–18 days). One patient died on day 4 of his ECMO run after withdrawal of support due to declining neurologic status secondary to a hemorrhagic

TABLE 2. ECMO Circuit and Flow Characteristics

Circuit Details	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
ECMO modality	VV	VV	VV	VV	VV	VV
Cannulas						
Drainage/outflow cannula (location, size Fr)	R FV (25)	R FV (25)	R FV (25)	L FV (23/25)	R FV (25)	R FV (25)
Return/inflow cannula (location, size Fr)	R IJ (19)	R IJ (19)	R IJ (21)	R IJ (19)	R IJ (19)	R IJ (19)
Location patient cannulated	ICU	ICU	ICU	ICU	ICU	ICU
P:F ratio at time of cannulation	100	66	81	135*	98	91
Hemodynamics and flow characteristics						
Maximum values during first 7 d of run						
Plateau pressure (cm H_20)	27	23	30	27	30	29
Flow (L/min)	4.3	4.5	5.8	4.8	7	5
Sweep (L/min)	6	7	9	5	8	5
Sweep gas (%)	70	100	90	100	100	100
Median and IQR for first 7 d of run						
Plateau pressure (cm H_20)	26 (24–27)	21 (21–21)	30 (26–30)	24 (23.5–24)	23 (20.5–30)	29 (22–29)
Flow (L/min)	4.1 (4.1–4.2)	4.2 (4.1–4.5)	5.7 (5.5–5.8)	4.6 (4.3–4.7)	6.0 (5.9–6.1)	4.1 (4.1–4.9)
Sweep (L/min)	5 (4.5–5.3)	6 (4.5–7.0)	9 (8.0–9.0)	4 (3.8–5.0)	8 (7.0–8.0)	3 (3.0–4.0)
Sweep gas (%)	65 (55–70)	100 (95–100)	80 (70–90)	70 (70–90)	100 (100–100)	90 (73–95)

*P:F ratio was <100 at time of consultation.
ICU indicates intensive care unit; LFV, left femoral vein; RFV, right femoral vein; RIJ, right internal jugular vein; VV, veno-venous.

TABLE 3. ECMO Complications and Outcomes

	Frequency (n, %) n = 6
Complications	
Acute kidney injury (creatinine 3× baseline)	4 (67)
Peripheral vascular complication*	0 (0)
Renal replacement therapy	1 (17)
Sepsis/secondary infection (excluding pneumonia)	2 (33)
Bacteremia	0 (0)
Bleeding requiring transfusion	3 (50)
Neurologic (ischemic or hemorrhagic stroke)	1 (17)
Cannula dislodgement	0 (0)
Liver failure (Alanine aminotransferase [ALT] >5× upper limit of normal)	0 (0)
Circuit exchange (due to circuit thrombus)	1 (17)
Short term outcomes	
Survived to hospital discharge	1 (17)
Survived decannulation from ECMO	4 (67)
Died on ECMO	1 (17)
Remains cannulated with VV-ECMO	1 (17)

*Including limb ischemia and deep vein thrombosis.
VV ECMO indicates veno-venous extracorporeal membrane oxygenation.

cerebrovascular accident. One patient remains cannulated with VV ECMO at the time of this writing (Table 3). The most common ECMO complication thus far has been acute kidney injury in 4/6 (67%) and bleeding requiring blood transfusion in 3/6 (50%). Complications for the entire cohort are shown in Table 3.

CONCLUSIONS

In one of the first case series describing VV ECMO in severe COVID-19 related respiratory failure, we highlight outcomes from the first month of the pandemic at a major academic center in North America. Our program has supported several carefully selected COVID-19 patients to recovery, providing preliminary support for the role of VV ECMO in this pandemic. These initial results are an improvement from early international reports on ECMO use in COVID-19 patients where mortality rates were described to be as high as 50% with a range of 22–47 days on the circuit for patient who made it to decannulation.[6] It is notable that we are an established ECMO center, with longstanding experience treating patients with ARDS and highly experienced intensivists, respiratory therapists, nurses, and surgeons. Given increased care needs, exposure risks to health care staff are higher in ECMO patients, necessitating higher usage of PPE. Facing this new reality has been greatly facilitated by the commitment of our health system leadership to providing the training and equipment needed to protect team members.

These data are still very preliminary for this small cohort and long-term outcomes for COVID-19 VV ECMO patients remain unknown. Our optimism is tempered by a realistic appreciation for the comparative burden of providing VV ECMO for such long periods. ECMO is resource intensive and can impose strains on the infrastructural, human, and emotional capital of the hospital. The role of a regularly convening ECMO leadership team toward mitigating these tolls cannot be over-emphasized. Decisions for ongoing ECMO use must be made in the context of relative resource reserve and dynamic consideration of continued ability to address needs throughout the hospital. Indeed, there is a potential scenario where the health system is overwhelmed and ECMO must be abandoned to allow provision of basic services to more patients. However, in the absence of such extreme constraints, VV ECMO remains a fundamental rescue strategy for appropriately selected patients with severe ARDS due to COVID-19, and this early report demonstrates its feasibility and potential benefits.

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