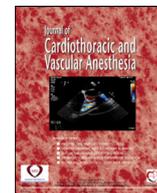


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## Letter to the Editor

**What is New in ECMO for COVID-19?***To the Editor:*

SARS-CoV-2 was declared a global pandemic on March 11, 2020, and has directly and indirectly resulted in significant changes to the practice of medicine.<sup>1</sup> COVID-19 can range in illness severity from asymptomatic to critically ill, with either acute respiratory distress syndrome (ARDS), cardiogenic shock, or both requiring extracorporeal membrane oxygenation (ECMO).<sup>2-4</sup> In general, pulmonary compromise is the most common abnormality in ECMO patients hospitalized with a primary diagnosis of COVID-19.<sup>5</sup> Since the beginning of the COVID-19 pandemic, ECMO (primarily for respiratory indications) has supported thousands of patients with COVID-19 who would otherwise not have survived.<sup>3,4</sup> With the ongoing pandemic and need for ECMO in select cases of severe COVID-19, updates are necessary for managing teams to provide optimal care.

**Cannulation Techniques**

With advances in the technology, multiple cannulation methods exist to support patients requiring ECMO. For venovenous ECMO (VV-ECMO), strategies include femoral-internal jugular, femoral-femoral, and single dual-lumen cannulae.<sup>6</sup> An additional dual-lumen single cannula strategy involves right atrial drainage with return to the pulmonary artery, offering right ventricular support with the option of ECMO. In a multicenter retrospective review of 435 COVID-19 patients undergoing VV-ECMO support published in February of 2022, the right atrial-to-pulmonary artery single-cannulation strategy significantly reduced mortality in comparison to the dual-cannula strategy (relative risk: 0.52).<sup>7</sup> This result may have biologic plausibility given the high incidence of right ventricular dysfunction in ARDS (upward of 50% in some studies).<sup>8,9</sup> Though limited by the retrospective nature, this work was an important first step in the search for whether an “optimal” cannulation strategy in ARDS exists. An additional report published in September of 2022 discussed the use of an ECMO configuration with a dual-circuit VV-ECMO approach, with bilateral femoral drainage cannulae each drained by independent circuits, which then reinfuse into a single, large right internal jugular vein cannula.<sup>10</sup> This

technique allows for higher flows and improved oxygenation and ventilation, which may be helpful in the case of patients with higher body mass index and cardiac output. Though retrospective, the available literature strongly points toward a survival benefit with the use of ECMO in patients with severe ARDS due to COVID-19, with one study suggesting a 7.1% absolute improvement in mortality with its use.<sup>11</sup> Additionally, survival may not be the only endpoint; extubation and mobilization in patients supported with VV-ECMO may be best achieved with single-cannula strategies, and this should be a consideration in trials or retrospective reviews comparing the efficacy of various cannulation strategies.

There are multiple approaches to the process of ECMO cannulation. Echocardiographic guidance and fluoroscopic guidance are both possibilities. Transesophageal echocardiography (TEE) is considered an aerosol-generating procedure and concern exists for the safety of proceduralists and other healthcare providers present during this semiinvasive procedure.<sup>12</sup> However, the act of transporting patients to an operating room or cardiac catheterization laboratory is also a risk to patients and those providing care in that setting, particularly during high-risk events such as ventilator switches. A retrospective review, published in July of 2022, of 107 patients with confirmed COVID-19 infection who underwent TEE-guided VV-ECMO cannulation, found the following: no TEE-related complications, no infections in healthcare workers, one cannulation-related pneumothorax (diagnosed by TEE), one femoral arterial injury, and one incident of failure to achieve proper wire position due to an anatomic abnormality discovered with TEE.<sup>13</sup> Additionally, multiple intracardiac thrombi or thrombi in transit (11 of 107 patients) and baseline pericardial effusions (11 of 107 patients) were discovered with the use of this imaging modality.<sup>13</sup> This real-world experience strongly supports the use of TEE to assist in deploying VV-ECMO. Additionally, TEE may be performed safely in the prone position to assess for abnormalities and assist in cannulation planning before supination.<sup>14</sup>

**Selection Criteria**

Extracorporeal membrane oxygenation is very resource-intensive, and patient selection has continued to be an ongoing challenge in all populations, with COVID-19 being no exception. With increasing experience and database size mounting,

an opportunity arises to assess which patients with severe COVID-19 may derive the most benefit from ECMO. A retrospective review published in May of 2022, examining 7,345 patients hospitalized with COVID-19, including 844 patients supported by VV-ECMO, found a 7% improvement in survival for the patients receiving VV ECMO.<sup>11</sup> The authors also found that age <65 combined with either PaO<sub>2</sub>/fraction of inspired oxygen ratio <80 or driving pressure >15 mmH<sub>2</sub>O were the patient groups most likely to benefit from VV-ECMO.<sup>11</sup> This large experience is invaluable in the patient selection process, and should be replicated for other common diagnoses with clinical constellations necessitating ECMO support.

### Special Populations

An important group to consider is the critically ill, pregnant and peripartum population, who require a level of multidisciplinary care like few other populations. The COVID-19 pandemic has significant implications for this unique patient population, with significantly higher morbidity and mortality in pregnant and peripartum patients diagnosed with COVID-19 by polymerase chain reaction.<sup>15</sup> The available literature on the use of VV-ECMO in pregnant and peripartum patients with ARDS due to COVID-19 suggests excellent outcomes.<sup>16,17</sup> A preliminary multiinstitutional case series, published in February 2021, of 9 pregnant or postpartum patients supported with VV-ECMO for COVID-19 ARDS, noted that 7 patients survived to discharge, with 2 patients who were still hospitalized at the time of publication.<sup>16</sup> An extracorporeal life support organization (ELSO) registry search, published in January of 2022, of 100 patients, reported an 84% survival to discharge, statistically significantly higher than nonpregnant female patients (84% v 51.5%).<sup>17</sup> Additionally, the pregnant and peripartum cohort had statistically significantly less acute kidney failure (13.0% v 25.1%).<sup>17</sup> Though retrospective, these reviews suggested that, as with other pathologies, VV-ECMO for refractory pulmonary compromise due to COVID-19 is a viable rescue option in pregnant and peripartum patients.<sup>18</sup>

### Thrombosis and Hemostasis

Bleeding and thrombotic events in patients supported by ECMO for pulmonary sequelae associated with COVID-19 are very common.<sup>19</sup> Specifically, one review published in August of 2022 that examined hematologic outcomes of 620 patients with COVID-19 supported predominantly by VV-ECMO (>92%) found 29% of patients had bleeding, 16% had thrombotic events, and 20% had both bleeding and thrombotic events.<sup>19</sup> Specifically, intracranial hemorrhage was noted in 8% of patients, and carried a nearly 14-fold increase in mortality.<sup>19</sup> In this study, oxygenator failure was noted in 9.5% of patients.<sup>19</sup> The treatment for progressive oxygenator clot burden traditionally has involved oxygenator exchange. One small case series published in August of 2022 explored a novel approach of injecting small doses (5, 10, or 20 mg) of recombinant tissue plasminogen activator in the drainage limb of

patients with rising transmembrane pressures and reduced, yet still viable, oxygenator function supported by VV-ECMO.<sup>20</sup> The authors found that tissue plasminogen activator administration resulted in prolonged oxygenator use and suggested that although more research is necessary, this technique may be considered in times of oxygenator shortage.<sup>20</sup> Caution and meticulous technique to avoid air entrainment is necessary with this approach, as injecting tissue plasminogen activator before the motor requires accessing the negative pressure portion of the ECMO circuit.

Acquired von Willebrand syndrome is a well-known phenomenon in patients supported by ECMO, and patients with COVID-19 supported by VV-ECMO also demonstrate this physiology.<sup>21</sup> In particular, a study published in August of 2022, assessing qualitative von Willebrand factor (vWF) activity in 27 patients supported by VV-ECMO, found that all patients had undetectable high-molecular-weight vWF multimers (the most active form) within hours of the initiation of support.<sup>21</sup> In a subset of 12 patients in this study, the use of desmopressin was not found to increase the concentration of high-molecular-weight vWF multimers.<sup>21</sup> After circuit discontinuation, the authors found that up to 38 hours had to pass before recovery of the biologically active high-molecular-weight vWF multimers.<sup>21</sup> The authors thus concluded that patients with COVID-19 suffering from bleeding complications, supported by VV-ECMO, would be better served with the use of products with vWF concentrates as opposed to desmopressin.<sup>21</sup> These results also suggested that it may be prudent to delay nonemergent procedures until approximately 2 days after VV-ECMO decannulation to reduce the risk of bleeding complications.

### Myocarditis

COVID-19–associated acute myocarditis is a rare entity (prevalence of approximately 0.25% per 1,000 hospitalizations) that may target younger patients.<sup>22</sup> In a study by Ammirati et al. published in April of 2022, concomitant COVID-19–associated pneumonia was found to significantly increase the risk of death in patients with COVID-19–associated acute myocarditis (15.1% v 0%).<sup>22</sup> The composite of in-hospital mortality or need for mechanical circulatory support was 20.4% in this cohort of 54 patients with definite or probable acute myocarditis.<sup>22</sup> Given the young age (median 38 years old) and high risk of adverse events in this population, an analysis of mechanical circulatory support outcomes in this patient cohort is key to inform decision-making regarding the use of venoarterial ECMO. A recent query of the ELSO registry published in August of 2022 found that among a cohort of 4,792 patients with sequelae of COVID-19 as the indication for ECMO support, 88 had a diagnosis of acute myocarditis.<sup>2</sup> Interestingly, not all of these 88 patients received cardiac support (53% received cardiac support and 42% received pulmonary support), and, as expected, the pre-ECMO respiratory parameters were better and the hemodynamic and metabolic parameters were worse.<sup>2</sup> Finally, mortality in the myocarditis cohort was 51%, which is in line with patients with primary

respiratory decompensation requiring ECMO.<sup>2</sup> In summary, from this limited data with a small population, the use of ECMO for patients with COVID myocarditis is an appropriate method of support with acceptable survival and should be used when indicated.

The COVID-19 pandemic continues to stress healthcare systems worldwide, and although vaccination has improved the burden of disease, patients continue to present with severe disease necessitating VV-ECMO support.<sup>23,24</sup> Literature on this patient population continues to evolve and, as a result, practice-changing research is released on a frequent basis. [Table 1](#)

contains the research highlighted in this work. Registries such as ELSO, the COVID-19 Critical Care Consortium Registry, and The Extracorporeal Membrane Oxygenation for Respiratory Failure and/or Heart failure related to Severe Acute Respiratory Syndrome-Coronavirus 2 have all been used to produce meaningful, potentially practice-changing literature. Registries also can serve the important purpose of analyzing data on special populations such as the pediatric and neonatal cohorts. Though more research is needed to validate the literature, with thoughtful consideration, knowledge acquired from studying patients with COVID-19 supported

Table 1  
Summary of Recent Literature on ECMO for COVID-19

Study Title	Study Type	Authors and Date Published	Practice Implication
Outcomes by cannulation methods for venovenous extracorporeal membrane oxygenation during COVID-19: A multicenter retrospective study	Retrospective	Saeed O et al. February 2022	Single cannula RA to PA strategy may be superior to other methods of ECMO for COVID-19.
Extracorporeal membrane oxygenation circuits in parallel for refractory hypoxemia in COVID-19: A case series	Retrospective	Patel YJ et al. September 2022	A dual circuit approach may be helpful in patients with blood flow limitations.
Transesophageal echocardiography-guided extracorporeal membrane oxygenation cannulation in COVID-19 patients	Retrospective	Castro et al. July 2022	TEE has guided ECMO cannulation, which has a low complication rate and diagnoses important pathology including pre-existing pericardial effusions and systolic dysfunction.
Venovenous extracorporeal membrane oxygenation in patients with acute COVID-19 associated respiratory failure: comparative effectiveness study	Retrospective COVID-19 Critical Care Consortium Registry Analysis Comparative Effectiveness Study	Urner et al. May 2022	The best outcome difference may be with ages <65 years old, P/F ratio <80, and driving pressures >15.
Pregnant and peripartum women with COVID-19 have high survival with extracorporeal membrane oxygenation: An Extracorporeal Life Support Organization Registry analysis	Retrospective ELSO Registry Analysis	O'Neil et al. January 2022	Pregnant and peripartum patients have higher survival rates and a lower incidence of renal failure than the nonpregnant population.
Bleeding and thrombotic events in patients with severe COVID-19 supported with extracorporeal membrane oxygenation: A nationwide cohort study	Retrospective ECMOSARS Registry Analysis	Mansour et al. August 2022	Over one-fourth of patients have bleeding issues, 16% had thrombotic issues, 20% had both, 8% had ICH, and 9.5% had oxygenator failure.
Injection of recombinant tissue plasminogen activator into extracorporeal membrane oxygenators postpones oxygenator exchange in COVID-19	Retrospective	Mang et al. August 2022	Injection of low dose tPA into an oxygenator may reduce the need for exchange but should only be considered in the case of oxygenator shortage.
Acquired von Willebrand syndrome and desmopressin resistance during venovenous extracorporeal membrane oxygenation in patients with COVID-19: A prospective observational study	Prospective Observational	Kalbhenn et al. August 2022	Acquired von Willebrand disease during ECMO support is ubiquitous and reverses in $\leq 38$ h after decannulation.
Outcomes after extracorporeal life support for COVID-19 myocarditis: An analysis of the Extracorporeal Life Support Organization Registry	Retrospective ELSO Registry Analysis	Tonna et al. August 2022	Clinically significant myocarditis due to COVID-19 is rare and carries a different clinical profile from COVID-19 pneumonia. With the use of ECMO, survival is acceptable and should be used if needed.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal life support organization; PA, pulmonary artery; P/F, ratio of partial pressure of oxygen to fraction of inspired oxygen on the ventilator; RA, right atrium; TEE, transesophageal echocardiogram; tPA, tissue plasminogen activator.

by VV-ECMO also may be applicable to other populations undergoing VV-ECMO support.

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