Toward Precision Delivery of Extracorporeal Membrane Oxygenation in Coronavirus Disease 2019 Cardiorespiratory Failure

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was officially declared a global pandemic on March 11, 2020, by the World Health Organization (WHO). The majority of patients with COVID-19 have mild disease, but approximately 14% develop severe respiratory failure and acute respiratory distress syndrome (ARDS), which is associated with high mortality.[1–3] Extracorporeal membrane oxygenation (ECMO) could potentially improve survival in COVID-19-associated severe ARDS and has been incorporated in the WHO recommendation for management of severe COVID-19 disease.[4–8]

In this issue of *ASAIO J*, Slepian *et al*.[9] report on the early experience of a multicenter cohort of patients undergoing ECMO for COVID-19 severe respiratory or cardiorespiratory failure. Their study, the largest cohort of COVID ECMO patients to date, describes 32 patients who were provided extracorporeal support either with veno-venous (VV), veno-arterial-venous (VAV), or veno-arterial (VA) ECMO. This initial description provides some insights into the use of ECMO for COVID-19 disease. Notably, the authors provide a glimpse at the median duration of ECMO in the five patients successfully weaned from ECMO (8 days, IQR = 6–10), in addition to spending several days in endotracheally intubated before initiation of ECMO (median = 4 days, IQR = 2–5). Further, there is a trend toward higher mortality in those patients who require VA-ECMO or VAV-ECMO, in contrast to those patients who only require VV-ECMO, which could potentially be explained by the concomitant cardiac component of their COVID-19 disease, as well as the likely low-flow state and end-organ hypoperfusion before initiating VA-ECMO.

However, as the authors note, outcomes are unclear from this cohort as the majority of the patients in the cohort were still receiving ECMO at the time of publication. The report is also limited in that detailed data on patient characteristics and detailed ventilatory data before the provision of ECMO are challenging to come by. These data will be crucial for further tailoring of both ECMO referral and cannulation criteria to identify those most likely to benefit from ECMO support.[9]

There is currently limited guidance on ECMO use and patient selection in a pandemic surge, particularly for COVID-19. The role of ECMO depends not only on patient factors (such as disease severity) but also on resource availability, as it consumes a large portion of hospital, critical care, and personnel resources.[10–13] Moreover, ECMO capacity at these levels of systemic stress may be very limited at centers capable of providing this technology. ECMO growth was catalyzed following the CESAR trial successfully demonstrating a mortality benefit in patients referred to an ECMO center for respiratory failure as well as the influenza A (H1N1) viral pandemic in 2009.[14–16]

Data on the effectiveness of ECMO during previous coronavirus outbreaks, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), remains limited, particularly during SARS. ECMO for MERS demonstrated an association with improved survival.[17] Based on this historical experience, it is plausible that ECMO may improve survival outcomes for selected COVID-19 patients with severe ARDS.

Given the significant resources required to provide ECMO, it is conceivable that during a pandemic it may become too burdensome to the system to be possible or justifiable. Principles of precision clinical medicine should be applied to patient selection and determining who is likely to most benefit from ECMO support during the COVID-19 pandemic.

Early reports have determined several patient factors that are associated with high mortality in COVID-19, which include advanced age (>65 years), presence of comorbidities, extrapulmonary organ failures (assessed through Sequential Organ Failure Assessment score), hyperinflammation (elevated C-reactive protein, ferritin, or D-dimer), leukopenia, and myocardial injury (elevated troponin).[18,19]

Patients with one or more of the aforementioned risk factors for poor outcomes are less likely to be successfully supported with VV-ECMO. Eligible patients who develop COVID-19-related myocarditis leading to refractory cardiogenic shock may benefit from VA-ECMO, shown to confer survival benefit in

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patients with isolated myocarditis.[20–22] Prospectively validated survival prediction models at ECMO initiation (*e.g.*, RESP and PRESET scores) can assist in the assessment of candidacy for ECMO; however, these scores have not specifically been validated for COVID-19-associated ARDS.[23,24]

Initial criteria for consideration for ECMO should be based on current evidence and guidance. Patients with very severe ARDS who have been invasively ventilated for 7 days or less meeting the EOLIA trial criteria and recent Extracorporeal Life Support Organization (ELSO) general guidance (ratio of arterial oxygen partial pressure to fractional inspired oxygen [P_aO_2:F_iO_2] <50 mmHg for >3 hours, or P_aO_2:F_iO_2 <80 mmHg for >6 hours or pH <7.25 with partial pressure of carbon dioxide [PCO_2] ≥60 mmHg for more than 6 hours)[5,10] without extrapulmonary organ failures could be considered for ECMO support.

It is likely that these criteria can be further refined. We know that VV-ECMO is able to provide two major benefits to patients with ARDS. The first is that it can improve oxygenation when the patient has exhausted conventional strategies.[5,25] The second, and likely more important mechanism, is that it facilitates extended lung-protective ventilation for patients who are already receiving conventional lung-protective ventilation. The EOLIA trial suggested that patients who were hypercarbic despite maximizing lung-protective ventilation were the group of patients with the greatest survival benefit that ECMO facilitates lung protection through a reduction in driving pressure and mechanical power.[5]

Patients with COVID-19-associated ARDS often present with notable hypoxemia, yet some may have relatively well-preserved lung compliance.[26] The majority of these patients could potentially be managed with conventional methods and without ECMO unless compliance worsens (*e.g.*, due to worsening underlying pathology, patient self-inflicted lung injury, or ventilator-induced lung injury) or hypoxemia is very severe and refractory to conventional management. These are the patients who are most likely to benefit from facilitated lung rest through VV-ECMO.

Given the complexity of patient selection, a multidisciplinary approach to patient selection should be undertaken. Collaboration between ECMO centers is crucial to ensure appropriate service delivery and capacity to those patients with confirmed COVID-19 ARDS. Thorough assessment before accepting a patient for ECMO will also ensure that ECMO should only be considered after all conventional measures (lung-protective ventilation, moderate-to-high levels of positive-end expiratory pressure as tolerated, prone positioning, possible neuromuscular blockade, and negative fluid balance, as appropriate) fail to maintain adequate oxygenation and ventilation.[27,28] Collaborative decision making between referring centers and the ECMO centers could potentially increase precision of clinical practice by reducing variabilities in the management of ARDS.

The decision to offer or decline ECMO during COVID-19 pandemic is a difficult one. ECMO centers need to be highly selective aiming to enhance the precision of individual treatment benefit. This approach will potentially allow judicious planning, resource allocation, and a safe delivery of ECMO service. Prospective data will enable clinicians to better characterize this disease and successfully personalize therapies including ECMO.

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