Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Pro and Con

Pro: Venoarterial ECMO Should Be Considered in Patients With COVID-19

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In a short period, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has devasted the world and has been responsible for more than one million deaths to date.[1] Although the most commonly reported severe symptoms include hypoxemia and respiratory distress, COVID-19 also is associated with involvement of other organ systems. Many aspects of the disease remain unknown; however, what has been well-established is that patients with underlying cardiovascular disease (CVD) are at an increased risk of death.[2] In patients in whom the cardiovascular system is affected severely, the authors believe that venoarterial extracorporeal membrane oxygenation (VA ECMO) should be considered for refractory cardiogenic shock.

COVID-19 and the Cardiovascular System

Understanding of the mechanism by which SARS-CoV-2 affects cardiac function only has had a few months to grow and to date remains incomplete. Data suggest that COVID-19 is associated with a severe systemic inflammatory response, resulting in a cytokine storm and the release of immune mediators.[3] Myocardial cells are at risk for direct injury from stress and increased oxygen demands in this environment. The renin-angiotensin-aldosterone system mediates fundamental processes in human physiology. It encompasses a sequence of vasoactive peptides necessary for vasomotor tone, blood pressure and fluid regulation, as well as vascular homeostasis.[4] Angiotensin-converting enzyme 2 (ACE2) receptor is an enzyme that breaks down angiotensin II and counteracts harmful effects, such as hypertension, tissue injury, and inflammation. Much like other coronaviruses, SARS-CoV-2 enters the body via these ACE2 receptors. These receptors are expressed highly on pulmonary alveolar cells but also exist, to a lesser extent, on vascular endothelial and myocardial cells. When the virus occupies these receptors, the disruption or downregulation of ACE2 receptor function can lead to a dysfunctional or nonfunctional renin-angiotensin-aldosterone system, which can have devasting effects on patients with COVID-19. Similarly, on a cellular level, SARS-CoV-2 activates the endothelium to upregulate von Willebrand factor and adhesion molecules, leading to recruitment of platelets and complement activation. Complement activation, combined with increased production and release of proinflammatory cytokines, lead to a highly thrombogenic state. Microvascular and macrovascular complications have been described, and can affect patients clinically with vascular thrombosis, coronary thrombosis, and pulmonary thrombosis.[5] Thrombotic complications have been reported in up to 31% of critically ill patients with COVID-19.[6] As a result of all of these factors, cardiac injury has been reported in 20% to 30% of patients to varying degrees.[7]

Cardiogenic shock, myocarditis, myocardial injury, cardiomyopathy, and cardiac arrhythmias all have been documented in COVID-19. It has been well-described that patients who have underlying CVD are at higher risk for morbidity and mortality.[8] A meta-analysis examined six studies including 1,527 patients with COVID-19. Of these patients, 17% had hypertension and 16% had CVD. Patients with these comorbidities were more likely to encounter severe disease and require intensive care treatment. Furthermore, the incidence of acute cardiac injury was at least 13 times higher in patients with severe disease than those with nonsevere disease.[9] Wang et al. retrospectively looked at 138 patients with COVID-19 in Wuhan, China, and found that 8% of patients developed shock, 7% had acute cardiac injury, and 16% had cardiac arrhythmias.

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Patients with the above cardiac involvement made up 30% to 40% of the patients who required transfer to the intensive care unit for advanced care.[10] In another cohort, Zhou et al. reported that 23% of 191 COVID-19 patients had heart failure. Of the 54 nonsurvivors in this cohort, the incidence of heart failure increased to 52%.[11] In many of these studies, the affected patients were not offered VA ECMO or other advanced circulatory support therapies. The mortality in the cohort of COVID-19 patients with concomitant heart failure is high, and the long-term cardiovascular effects remain unknown.[12] The literature continues to report a significant proportion of patients with cardiovascular complications; however, the role of VA ECMO and other circulatory support devices has yet to be established.

VA ECMO for Cardiogenic Shock

Patients suffering from cardiogenic shock carry a very high mortality without intervention. Mechanical circulatory support, specifically the use of VA ECMO, has become more widely used to help improve survival. Most studies quote 40% to 45% survival to hospital discharge after VA ECMO; however, pre-ECMO initiation risk factors such as younger age, lower weight, and reversible diagnoses such as acute myocarditis or arrhythmias, have better outcomes.[13] Although most studies report 90-day survival as the benchmark, others show favorable long-term survival at up to three years after discharge.[14] The Extracorporeal Life Support Organization (ELSO) guidelines for adult cardiac failure maintain that VA ECMO should be considered in patients with cardiogenic shock and inadequate tissue perfusion despite adequate intravascular volume, inotrope and vasopressor administration, and intra-aortic balloon pump support. Septic shock also is considered an appropriate indication. Patients for whom VA ECMO should not be considered include those with advanced age, chronic organ dysfunction, and prolonged resuscitation efforts without adequate tissue perfusion, and those who are deemed unrecoverable from a cardiac standpoint and are not considered candidates for advanced durable therapies.[15] Evidence supporting early rather than delayed initiation of VA ECMO from cardiogenic shock has been established and is associated with increased survival.[16] As one can imagine, these guidelines and recommendations are open to interpretation, and are highly dependent on the infrastructure that exists within the institution. VA ECMO requires a group of highly specialized providers and is often resource-intensive.

VA ECMO for COVID-19

Based on current knowledge of the disease, the question is not can COVID-19 patients be offered VA ECMO, but rather should COVID-19 patients be offered VA ECMO? The strategies for implementing VA ECMO have improved dramatically over the years. Peripheral cannulation techniques can be achieved promptly and efficiently at the bedside or even in the field. The inflow or venous cannula is situated in the right atrium and serves to decompress and support the right ventricle, which is helpful in patients with acute pulmonary emboli. Because VA ECMO bypasses not only the heart but also the lungs, it is of particular benefit in patients with COVID-19 to overcome respiratory failure, a hallmark of this illness.

Chow et al. have used the limited literature available to formulate considerations and recommendations for instituting VA ECMO in COVID-19 patients. Their highest-priority patients include the young, the critically ill, those with the greatest perceived benefit and fewest or no comorbidities, as well as healthcare workers. They recognized that the decision to place a patient on VA ECMO should be made on an individual basis and with a multidisciplinary team approach.[17] In other words, the recommendations for placing a COVID-19 patient on VA ECMO should be made according to the standards previously set by the ELSO.[18] They acknowledged that a patient who is receiving cardiopulmonary resuscitation actively should be placed on VA ECMO only at experienced institutions to minimize the risk of COVID-19 exposure and cross-contamination.[17] The official consensus guideline from the ELSO suggests that if a center has the resources and experience, the decision to place a COVID-19 patient on VA ECMO should be made on a case-by-case basis, and avoided if the patient is of advanced age, has multiple comorbidities, or presents with multisystem organ failure.[18] The authors recognized the substantial risk of bleeding and thrombosis with the use of VA ECMO, but this risk is true of all comers with cardiogenic shock, and is not specific to those with COVID-19.

Admittedly, the literature either supporting or discouraging the use of VA ECMO for COVID-19 patients is scarce. The complexity of this disease continues to evolve, and further investigation is warranted to identify whether select patients are appropriate for this resource-intensive therapy. Only a handful of studies have reported the use of VA ECMO in the COVID-19 population. Barbaro et al. looked at the ELSO registry and described the experience of 1,035 patients with COVID-19 who received ECMO. Most patients (94%) received venovenous ECMO (VV ECMO) for respiratory failure and only 4% of patients received VA ECMO for cardiopulmonary collapse. In-hospital mortality for all comers with COVID-19 was high at 37%, and for those who received VA ECMO it was even higher. Other risk factors included advanced age, acute kidney injury, immunocompromised patients, and those who received cardiopulmonary resuscitation prior to cannulation.[19] Although the increased risk associated with VA ECMO in this cohort was high, the authors believe that the small sample size was a considerable flaw in the analysis. Furthermore, this study affirmed the authors' previously noted statement that patients who are older and with significant comorbidities are likely poor choices for advanced support.

As the medical world is learning more about the disease, an increased number of centers are providing case reports of successful VA ECMO implementation and outcomes. The authors believe that as novel therapies continue to develop and patients with COVID-19 have improved survival, VA ECMO for cardiopulmonary failure likely will become a favorable

intervention. Bemtgen et al. described a case in which a 52-year-old man with COVID-19 presented with respiratory failure as well as mixed cardiogenic and vasoplegic shock. The patient recently had a myocardial infarction and was treated with a combined approach of Impella CP placement plus peripheral VA ECMO. On day seven, the patient was transitioned from VA ECMO to VV ECMO following resolution of cardiogenic and vasoplegic shock. On day 19, the Impella CP was removed. The patient remained on VV ECMO for respiratory failure and his cardiac function continued to improve.[20] Akoluk et al. report the case of a 50-year-old man who presented with cardiac arrest, fever, and hypoxemia and was COVID-19 positive. The patient had return of spontaneous circulation upon arrival and was found to have large saddle pulmonary emboli and bilateral ground-glass opacities in his lung fields. He was hemodynamically unstable on multiple vasoactive agents, and the decision was made to place him on VA ECMO early. While on VA ECMO, the patient received catheter-directed thrombolysis and on hospital day six, he was liberated from mechanical support. Despite the risk, the authors felt the patient's condition was reversible, and on hospital day 22 he was discharged home on anticoagulation.[21] Both patients received VA ECMO prior to developing irreversible multisystem organ failure and thus had favorable outcomes. The authors' institution also recently placed a young man with cardiogenic shock on VA ECMO. He presented with combined respiratory and cardiac failure and likely had COVID-19 myocarditis. The patient survived without significant end-organ dysfunction and was decannulated within ten days of VA ECMO institution. In the above examples, a careful balance of resource allocation with a thoughtful consideration of individual patient factors were implemented and led ultimately to successful outcomes.

Although the authors support the use of early VA ECMO for refractory cardiogenic shock in COVID-19 patients, there is another scenario that currently is unfolding at experienced centers that offer VV ECMO. The nature of the disease is such that respiratory failure from ARDS without cardiogenic shock commonly may be encountered in critically ill patients. These patients may be placed on VV ECMO with variable success and often for extended periods. During this time of support, patients subsequently may develop cardiac failure. For this reason, an increasing number of centers are transitioning these patients from VV to VA ECMO. Henri Mondor Hospital notes that of the 50 patients who required ECMO support for COVID-19, 7 patients necessitated a change in strategy to VA ECMO for either cardiac arrest during cannulation or development of pulmonary embolism or myocarditis while on VV ECMO support. This hospital serves as an ECMO referral center in Paris and has the infrastructure, personnel, and resources to offer heroic interventions and a chance of survival and recovery.[22] This example highlights a further consideration for institutions willing to offer VV ECMO to COVID-19 patients. If they are equipped with the infrastructure and resources to offer VV ECMO for respiratory failure, should not they also be prepared to offer VA ECMO if the situation changes? Literature surrounding this question is essentially nonexistent but requires further investigation.

The medical world's response to the pandemic caused by SARS-CoV-2 can be described best as adaptive, innovative, and resilient. The complexities of COVID-19 continue to evolve, and many questions about the pathophysiology of the disease remain unanswered. It has been well-established that patient factors such as increased age, underlying CVD, and secondary infections, are associated with an increased risk of mortality.[23,24] The use of VV ECMO for COVID-19 has been reported consistently for the treatment of respiratory failure but with variable success.[25,26] What remains in question is the role of VA ECMO when patients develop refractory cardiogenic shock. It is the authors' opinion that the decision to implement VA ECMO for COVID-19 should be based on the same criteria that experienced centers use for all comers with cardiogenic shock. VA ECMO is complex and requires experienced personnel, and its implementation is a decision that always should be made with a multidisciplinary team approach, taking individual patient factors into consideration. Based on current knowledge of the effects of COVID-19 on the cardiovascular system, it is the authors' opinion that otherwise suitable candidates who develop refractory cardiogenic shock should be considered for VA ECMO to provide them a fair chance for a full recovery.

Conflict of Interest

None.

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