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

Con: Venoarterial ECMO Should Not Be Considered in Patients With COVID-19

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THE RESPONSE to coronavirus disease 2019 (COVID-19) has involved a rapid global effort to understand the behavior of this disease, the range of clinical manifestations, and effective treatment modalities. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and was declared a pandemic on March 11, 2020 by the World Health Organization.[1] Since the identification of symptoms in the first documented case in December 2019, there have been more than 40 million confirmed cases and one million confirmed deaths worldwide as of the writing of this article,[2] with an estimated mortality rate of 1.5% to 3.6%.[3]

Clinically, COVID-19 is associated with a range of presentations—from asymptomatic to mild respiratory symptoms, through severe multiple organ failure. Moderate-to-severe disease typically is associated with fewer respiratory symptoms, less pulmonary failure, and less acute respiratory distress syndrome (ARDS). The mainstay of treating COVID-19–induced respiratory failure consists of supportive care, pharmacologic treatment, and protective mechanical ventilation. Compared with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus, patients with COVID-19 are more likely to experience cardiovascular complications.[4] This raises the question of which therapies are most effective in cardiogenic shock secondary to COVID-19.

Although the use of venovenous extracorporeal membrane oxygenation (VV-ECMO) has been reported many times in the literature for refractory COVID-19 respiratory failure,[5,6] reports of venoarterial extracorporeal membrane oxygenation (VA-ECMO) have been sparse. VV-ECMO has been demonstrated to improve mortality in patients with severe hypoxic respiratory failure refractory to protective mechanical ventilation alone.[7,8] However, VA-ECMO only has been used in 4% of all patients with COVID requiring ECMO,[8] and the benefit is less clear. The authors argue that at this time, save for exceptional circumstances, VA-ECMO should not be used for COVID-19 patients in cardiogenic shock.

Cardiovascular Collapse Typically Occurs in Conjunction With Multiorgan Dysfunction

Cardiovascular shock in COVID-19 is understood poorly, but likely is due to one or more of several mechanisms: exacerbation of underlying cardiovascular disease, viral myocarditis, cytokine-induced myocardial stress, or right heart failure secondary to pulmonary venous thrombosis.[9-13] Cardiac complications of COVID-19, while not as common as respiratory symptoms,[14] do occur with some frequency and lead to increased morbidity and mortality. The rate of heart failure in hospitalized COVID-19 patients has been reported at 24%,[15] while clinically identified shock may occur in 9-to-17% of patients.[15,16] Cardiac injury, as identified by highly elevated levels of high-sensitivity troponin, is associated independently with increased mortality,[14,17,18] and patients with a history of hypertension, diabetes, and prior cardiac disease are at increased risk of cardiac injury while hospitalized with COVID-19.[14] Additionally, COVID-19 patients identified with cardiac injury have more complicated hospital courses, including increased incidences of mechanical ventilation, ARDS, acute kidney injury, and coagulation disorders.[14]

Microvascular thrombosis leading to myocardial dysfunction also has been suggested as an etiology; however, direct pathologic evidence of this appears lacking.[12] The incidence of right ventricular (RV) dysfunction in COVID-19 may be underestimated clinically,[19] with a reported frequency of RV abnormalities of 32% to 39% in hospitalized patients.[20,21] This should not be surprising, given that prior to the COVID-19 pandemic, RV dysfunction has been shown to occur frequently (22%-50%) in moderate-to-severe ARDS.[22] This association between RV dysfunction and ARDS may be attributed, at least

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in part, to elevated pulmonary vascular resistance with severe respiratory disease. Additionally, the high incidence of venous thromboembolism (23%-27%) in COVID-19 is likely to induce RV dysfunction in a subset of affected individuals.[23,24] Finally, there have been clinical case reports of stress-induced cardiomyopathy in COVID-19 patients.[25,26]

In addition to the increased mortality associated with cardiac injury in COVID-19, a few factors are worth considering prior to initiating VA-ECMO for COVID-19 patients in shock. First, preliminary numbers on the efficacy of VV-ECMO report a mortality of 57%,[27] which is already higher than the 35% mortality seen in the ECMO to Rescue Lung Injury in Severe ARDS trial.[28] The exact reasons for this discrepancy are elusive; however, the multiple organ involvement seen in severe SARS-CoV-2 infection is a probable etiology. When employing the more complicated cannulation strategies typically associated with VA-ECMO, the mortality rate only will rise. Since mortality with the utilization of VA-ECMO in the absence of COVID-19 is already higher,[29] COVID-19 VA-ECMO mortality can be expected to exceed at least 60%.

Most COVID-19 patients presenting with cardiac complications have contraindications to VA-ECMO. The Extracorporeal Life Support Organization (ELSO) released a guidance document regarding the use of ECMO in COVID-19 patients.[30] Notable relative contraindications to the initiation of ECMO outlined in this document included advanced age, significant comorbidities, and more than seven days on mechanical ventilation. Patients who fit into one or more of these categories can be expected to derive a diminished benefit from ECMO due to a higher risk of mortality, with multiorgan failure being the most common cause of mortality on VA-ECMO.[29] As noted previously, COVID-19 patients presenting with acute cardiac injury are in fact more likely to have underlying cardiovascular comorbidities and be of advanced age,[14] factors that no doubt contribute to an increased mortality risk,[15-18,21,31-33] and, the authors argue, represent contraindications to the use of VA-ECMO.

With the high prevalence of ARDS among hospitalized COVID-19 patients—33% of hospitalized COVID-19 patients and 75% of COVID-19 patients in the intensive care unit (ICU)[34]—the additional finding of cardiogenic shock and its sequelae typically will qualify a patient for the diagnosis of multiple organ dysfunction syndrome. Furthermore, the authors posit that severe ARDS, with its associated increase in RV afterload, is likely the most common contributor to cardiovascular collapse in COVID-19 patients admitted to the ICU. Pagnesi et al. found that in COVID-19 patients not admitted to the ICU, the prevalence of pulmonary hypertension was 12% and associated with increased mortality.[35] This information, combined with the finding that mortality also is increased in COVID-19 patients found to have RV dilation on admission,[20] suggests that subclinical RV strain is occurring at a high rate among hospitalized COVID-19 patients.[36] The presence of elevated pulmonary pressures in the highly proinflammatory setting of severe COVID-19 disease is likely to blame for increased RV strain that progresses to frank RV failure if pulmonary recovery is not achieved in a reasonable time frame. Overt RV dysfunction typically is seen as a late finding that heralds cardiovascular collapse.[21,37] This fits with a prior investigation that showed RV dysfunction to be associated independently with mortality in ARDS.[38]

Predictors of outcome with VA-ECMO, such as the Survival After Veno-Arterial ECMO score, do exist[39]; however, their applicability to this current pandemic is difficult to ascertain, and the score may not function as intended in this atypical patient population. Further analysis of the ELSO COVID-19 ECMO registry may shed light on the utility of VA-ECMO in this disease;[30] but until such a time, the authors favor sparse application of VA-ECMO to patients presenting with COVID-19 cardiogenic shock.

Investigating the limited data on management of cardiogenic shock in COVID-19 reveals numerous case reports of successful shock management using pharmacologic support without the use of ECMO.[26,40,41] Conversely, the few case reports that exist describing VA-ECMO use in COVID-19[26,42-44] show a mortality rate of 75% to 100% (three of four patients, with one patient still on VV-ECMO at the time of case report release), highlighting the advanced disease state that most commonly is present in COVID-19 patients who fail pharmacologic circulatory support.

Therefore, the authors believe that patients who present with respiratory failure and then progress to circulatory failure should be diagnosed with multiple organ dysfunction syndrome and not offered VA-ECMO. Furthermore, patients who present in cardiogenic shock with respiratory failure of noncardiogenic etiology similarly should not be considered for mechanical circulatory support.

Coagulopathy

Patients with SARS-CoV-2 have an increased risk of developing a hypercoagulable state, which manifests with the formation of both macro- and microvascular thrombi.[45] Macrovascular thrombi in patients with SARS-CoV-2 most commonly manifest as deep vein thromboses and pulmonary emboli, which are described as occurring in 20% to 30% of patients with SARS-CoV-2 who are admitted to the ICU.[24] Other manifestations of hypercoagulability include instances of ventricular thrombi[46] and thrombus formation in extracorporeal circuits. Thrombosis in the ECMO circuit typically accumulates at the level of the oxygenator, resulting in a progressively increasing resistance to flow, decreased gas exchange, and, ultimately, failure of the ECMO circuit.

Patients with SARS-CoV-2 often have demonstrated hypercoagulability despite receiving therapeutic levels of anticoagulation.[47] The doses of anticoagulant required to overcome this degree of hypercoagulability may confer a higher risk of life-threatening bleeding. Patients who have developed cardiogenic shock as part of the SARS-CoV-2 syndrome typically experience dysfunction of other end-organs. As described by the ELSO, multiorgan dysfunction is considered a contraindication.[29]

Resource Intensive

Due to the extent of the pandemic, it is particularly important that resources are distributed in a manner that enables equitable access to the most effective therapies for as many

patients as possible. Extracorporeal membrane oxygenation is extremely resource-intensive, diverting time, money, equipment, and personnel that may be used more effectively to provide care for a greater number of critically ill patients.

The ELSO guidelines support the use of VA-ECMO in patients in whom cardiogenic shock is refractory to medical therapies. However, the list of contraindications is comprehensive and includes advanced age, comorbidities, and absence of an exit strategy after ECMO.

Initiation and management of VA-ECMO require surgeons and/or other physicians adept at cannulation, staff skilled in the 24-hour monitoring of patients receiving ECMO therapy, a critical care bed space and ECMO circuit, oxygenator, ECMO pump plus backup pumps to ensure redundancy. Even in the United States, where ECMO is used more frequently per capita than in any other country, this is a finite resource. The incidences of pathologies that have required VA-ECMO prior to the COVID-19 pandemic have not become rarer, and the upscaling of ECMO device availability is expensive and slow. Hospitals already are experiencing shortages in the availability of ECMO circuits for patients requiring V-V ECMO. Therefore, it is challenging ethically to suggest the diversion of a finite resource for a patient group who have an unclear benefit from VA-ECMO.

ECMO is a highly technical therapeutic modality, and outcomes have been demonstrated to be correlated strongly to the frequency with which ECMO is used by a hospital. Therefore, in the cases in which VA-ECMO is being considered, to ensure the highest chance of a positive outcome the patient should be transferred to a center with an established ECMO program. However, this is problematic, as ECMO centers already are experiencing increased demand for VV-ECMO.

Conclusion

Patients with COVID-19 who develop cardiovascular collapse are treated most effectively and efficiently with supportive medical therapies. Mechanical circulatory support with VA-ECMO is extremely resource-intensive, and is contraindicated in most patients with COVID-19 due to the presence of multiorgan dysfunction. Right ventricular dysfunction due to severe respiratory failure is a common cause of late cardiovascular collapse in COVID-19, and represents end-stage disease not amenable to mechanical circulatory support. The authors recommend that VA-ECMO be reserved for the rare cases of patients with COVID-19 who present with isolated myocardial dysfunction, and be offered only in centers experienced at providing VA-ECMO.

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