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Mechanical Circulatory Support in COVID-19

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KEYWORDS

• COVID-19 • Cardiogenic shock • Mechanical circulatory support
• Extracorporeal membrane oxygenation • Acute respiratory distress syndrome

KEY POINTS

- Patients with cardiogenic shock or acute respiratory distress syndrome experience high rates of morbidity and mortality
- Concomitant COVID-19 infection significantly increases risks of complication and death for these patient populations
- The application of mechanical circulatory support technology for patients with COVID-19 infection has the potential to save lives but also brings with it high rates of complications and mortality
- Careful patient selection, diligent management, and a team-based approach are critical to improving outcomes in this challenging patient population
- More research is needed to improve our understanding of which subset of COVID-19 patients may benefit from cardiopulmonary mechanical support

INTRODUCTION

Cardiogenic shock (CS), a devastating complication of acute myocardial infarction (AMI) and other cardiac disorders, is a state of end-organ dysfunction that occurs in the setting of inadequate cardiac output. Despite advances in diagnostic technology, upfront revascularization strategies, and aggressive medical management, CS remains a highly morbid condition fraught with complications and high rates of mortality.[1–3] Mechanical circulatory support (MCS)—to include percutaneous right- and left-ventricular support devices, including extracorporeal membrane oxygenation (ECMO)—offers an additional level of support for select patients, but a standardized approach to the application of this technology remains challenging, partially due to the inherent difficulties with randomized controlled trials in this heterogeneous and complex patient population.[4,5] However, observational and cohort data from several institutions have shown the utility of the thoughtful application of MCS technology based on objective criteria, invasive monitoring devices, and a multidisciplinary shock team approach.[6,7] The range and diversity of MCS devices has ushered in a new era for patients with CS, but recently clinicians have been faced with a new challenge: a global pandemic. Coronavirus disease 2019 (COVID-19) has challenged our understanding of cardiopulmonary physiology and brought with it unique challenges in a resource-limited environment. Although the primary effect of COVID-19 is on the respiratory system, its deleterious

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consequences have the potential to reach across all organ systems and can adversely affect cardiac function. This review article focuses on our current understanding of the effects of COVID-19 in the adult population as it pertains to CS, the assessment and evaluation of these patients, and the implementation of MCS in patients with cardiac or pulmonary failure, to include both venoarterial (VA) and venovenous (VV) ECMO.

PATHOPHYSIOLOGY AND EPIDEMIOLOGY

Although the pulmonary complications are well-described,[8] COVID-19's deleterious effects are not limited to the lungs. Any organ system, including the cardiac and vascular systems, can be involved, and the presentation of a patient with COVID-19 is often heterogeneous. Although overall rare, patients with COVID-19 can and do experience cardiovascular complications without concomitant pulmonary disease, and it is been shown that COVID-19 patients with underlying cardiovascular comorbidities experience increased morbidity and mortality.[9] Direct cardiovascular complications may occur in isolation, but it is also not uncommon that shock in the setting of COVID-19 is multifactorial and occurs on a spectrum, and includes noncardiac sources of cardiovascular collapses, such as inflammatory and distributive shock.

COVID-19's direct effects on the cardiovascular system are myriad and can include myocardial ischemia, direct cardiomyocyte injury (eg, myocarditis), or isolated right ventricular dysfunction. Although not fully understood, proposed mechanisms for ischemia in COVID-19 patients include virus-mediated macrocirculatory and microcirculatory thrombosis, endothelial dysfunction, and hypercoagulability,[10,11] and can cause a similar phenotype of CS as is seen with classical AMI.[12] Although rare, COVID-19 infection is associated with an increased risk of myocarditis, and in extreme cases can lead to CS refractory to medical management alone.[13–15] Right ventricular (RV) dysfunction, the most common cardiac manifestation of COVID-19 infection in some studies,[16] may be due to the indirect effects of hypoxia, pulmonary emboli, or primarily elevated pulmonary vascular resistance, and can lead to isolated RV failure or biventricular failure (see David W. Louis and colleagues' article, "The Cardiovascular Manifestations of COVID-19," in this issue).

Although most patients with COVID-19 may not experience these complications—or will remain relatively asymptomatic from cardiac complaints[17]—, for select patients, COVID-19 can lead to or precipitate refractory CS. For patients presenting with acute coronary syndrome, the presence of concomitant COVID-19 infection confers a significantly increased risk: patients are presenting later, have a higher risk of developing shock, and have a significantly higher mortality rate. In one prospective registry study, mortality for patients with concurrent COVID-19 and ST-segment elevation myocardial infarction (STEMI) approached 23%, compared with a non-COVID risk of approximately 5%, conferring an odds ratio of 3.33.[18] In the same registry, CS occurred 20% of the time in COVID-19 STEMI patients, compared with 8.7% in controls. The results of the North American COVID-19 ST-Segment Elevation Myocardial Infarction (NACMI) registry were even more sobering: COVID-19 patients presenting with an STEMI experienced a 33% mortality rate, compared with 4% seen in non-COVID-19 controls, with a significantly increased rate of CS at 18%.[19] Although the cause for this disparity is unclear, proposed mechanisms include delayed presentation secondary to reluctance to go to the hospital during a pandemic, prolonged ischemic time, and potentially intrinsic factors of COVID-19 infection, including proinflammatory and prothrombotic effects. Looking at all patients with COVID-19, despite being the most infrequent etiology of shock seen in admitted patients, CS portends the highest mortality of any shock state.[20] As such, its timely recognition, diagnosis, and treatment remain of utmost importance, especially within a cohort of patients critically ill with COVID-19.

DIAGNOSIS AND INITIAL MANAGEMENT OF COVID-19 PATIENTS WITH REFRACTORY CARDIOGENIC SHOCK

Although there is some variability in definition, the diagnosis of CS is classically described as systolic hypotension (SBP < 90 mm Hg or the use of vasopressors) in conjunction with signs of end-organ hypoperfusion in the setting of a reduced cardiac index of less than 2.2 L/min and an elevated pulmonary capillary wedge pressure of greater than 15 mm Hg.[3,21,22] This definition does not describe all phenotypes of CS, and, if stringently applied, may not capture all COVID-19 patients with CS, who may be more likely to present with lower filling pressures due to concomitant distributive shock.[20] For all patients, alternate surrogate markers of shock may be useful, such as cardiac power output or pulmonary artery pulsatility index, and use of the Society for Cardiovascular Angiography and Intervention (SCAI) classification scheme for CS should be considered.[4,5,22,23] Regardless, the diagnosis of CS often requires both noninvasive and invasive hemodynamic

assessment, including the placement of a pulmonary artery catheter, which has been shown to improve outcomes in patients with CS.[7] Given the relative infrequence of CS as an etiology of shock in the undifferentiated patient—especially for those patients critically ill with COVID-19—a high index of suspicion for a cardiac etiology of hemodynamic instability is of the utmost importance on the part of the clinician.

As randomized clinical trial data for the application of MCS in COVID-19 patients are sorely lacking, extrapolation from the traditional body of evidence for the application of MCS in CS is necessary. For COVID-19 patients experiencing AMI, early revascularization and standard medical therapy is warranted. For AMI and other etiologies of CS, subsequent medical management may include treating the precipitating insult as well as the use of volume expansion or the addition of vasopressors or inotropes. However, for many patients with CS of any etiology, medical management alone is not sufficient.[5] The decision to escalate to mechanical support for a patient with CS, as well as the selection of a device platform, may be both institution- and patient-specific. Patients with CS may present with isolated left or right ventricular failure, biventricular failure, or have challenges with oxygenation. Options for MCS include the intra-aortic balloon pump (IABP; Getinge, Sweden; Teleflex, Wayne, PA), percutaneous left ventricular assist devices such as the Impella (Abiomed, Danvers, MA), right ventricular support devices with or without oxygenators, and VA ECMO. Algorithms have been proposed to help standardize and guide the application of support devices for this challenging patient population,[4,5,24] and the use of objective criteria for the timing of application of MCS is encouraged, as it may improve survival.[25] In general, the guiding principles for success in MCS include appropriate patient selection, meticulous technical deployment, and diligent management in the cardiac intensive care unit with a multidisciplinary shock team.[5,24] Patients with COVID-19 and CS present unique challenges to an already complex and critically ill patient population, the anticipation of which can help guide the clinician caring for these patients on MCS.

MECHANICAL CIRCULATORY SUPPORT IN COVID-19: OUTCOMES AND CONSIDERATIONS

Circulatory Support

For COVID-19 patients suffering from myocardial infarction, the limited data available suggest a significantly increased mortality rate, especially for those who require some type of MCS. Data from the NACMI registry showed an almost 60% mortality rate in COVID-19–positive STEMI patients who required MCS, compared with a 30% mortality rate in non-COVID STEMI patients on MCS.[26] In this registry, 13% of COVID-19–positive STEMI patients received MCS, similar to rates seen in the non-COVID-19 population, highlighting the significant increase in mortality that a concomitant COVID-19 infection conferred. Within the COVID-19 group, the most prevalent type of MCS was the IABP (62%), followed by Impella (28%) and ECMO (7%). Data for or against a particular MCS strategy is limited by the lack of high-quality evidence in the CS patient population. Although the IABP remains commonly used for CS patients requiring MCS, longitudinal data have confirmed that these devices do not confer a mortality benefit.[27] Percutaneous left ventricular assist devices such as the Impella have shown some improvement in small clinical trials and registry data, although the evidence remains mixed and definitive research is ongoing.[28] For these strategies in COVID-19 patients, the data are even more scarce. Case reports exist of using IABPs or Impellas to support hemodynamics in patients with COVID-19 and CS, with mixed outcomes.[12,29]

VA ECMO for cardiovascular collapse in the COVID-19 population represents the maximal level of support possible and brings with it a high rate of morbidity and mortality—so high, perhaps, that many centers may not offer it in this patient population. Indeed, the Extracorporeal Life Support Organization (ELSO) cautions centers about performing extracorporeal cardiopulmonary resuscitation (defined as the insertion of VA ECMO in patients who are pericardiac arrest) on patients with COVID-19, especially in less experienced centers, because of both the technical complexity of the procedure and the risk of cross-contamination to staff.[30]

For COVID-19 patients requiring cardiac support with VA ECMO, ELSO guidelines suggest judicious patient selection in a multidisciplinary manner. Like all MCS, VA ECMO is not a definitive treatment, but is instead a bridge to a destination, be it recovery, durable ventricular assist device, or transplant. Patients with multisystem organ failure, significant medical comorbidities, or advanced age likely do not benefit from VA ECMO support, even without the added complication of an active COVID-19 infection.[31] Some presentations of CS portend slightly better prognoses (eg, myocarditis), whereas other patients with concomitant distributive or inflammatory shock will likely have worse outcomes. On the whole, the decision to place any patient—especially those with an active

COVID-19 infection—on VA ECMO should be a thoughtful, team-based decision with a clear exit strategy in mind. Some centers describe an algorithmic approach to MCS in these patients, favoring the initiation of V-A-V ECMO in COVID-19 patients with CS and refractory hypoxemia,[29] although survival rates of this strategy are unknown.

Overall, data on outcomes for patients with COVID-19 requiring VA ECMO for CS are extremely limited.[31] A large retrospective review of ELSO data found that VA ECMO represents a significant minority of all COVID-19 ECMO cases, perhaps as low as 4%, but is associated with a significantly higher in-hospital mortality rate compared with COVID-19 patients on VV ECMO.[32] ELSO itself does not directly report COVID-19 VA ECMO survival on its public dashboard, but at the time of publication, the survival rate to discharge in the COVID-19 non-ARDS adult cohort is less than 10%.[33] The EuroELSO survey of adult COVID-19 patients in Europe demonstrates a significant decline in the application of VA ECMO in this patient population as the pandemic has progressed, with VA ECMO representing 9% of all COVID-19 ECMO cases at the onset of the pandemic, but falling to an average of 4% during the fourth wave.[34]

The remainder of our current data is limited to case series and case reports, most of which report significant mortality rates for VA ECMO in COVID-19, far above prepandemic benchmarks.[35] Although more information is certainly needed about this patient population to guide thoughtful application and patient selection, it can be said that mortality rates for COVID-19 patients requiring any degree of MCS are high, and VA ECMO portends an even higher risk of death. Centers and clinicians who choose to pursue any MCS strategy in COVID-19 patients must do so thoughtfully and selectively, understanding the inherent risks and resources required.

Respiratory Support

For patients with severe acute respiratory distress syndrome (ARDS), be it from COVID-19 or another pulmonary insult, VV ECMO remains a salvage and off-label therapy for lung rescue for certain patient populations. The largest randomized controlled trial investigating VV ECMO for severe ARDS, conducted in the pre-COVID-19 era, was technically a negative trial,[36] although meta-analyses have shown some benefit for VV ECMO for refractory ARDS,[32] and subsequently its use in the adult population has increased significantly over the past 20 years. Although there are no universal guidelines, inclusion criteria from the EOILA trial are often used to evaluate VV ECMO candidacy, and include a Pao_2:Fio_2 ratio of less than 50 mm Hg despite maximal medical therapy for ARDS or a refractory respiratory acidosis.[36] According to the ELSO registry, ARDS patients requiring VV ECMO in 2018 had an overall survival rate of approximately 62%.[37] It is understandable, then, that VV ECMO posed an attractive option for patients with severe COVID-19–related ARDS at the beginning of the pandemic, when initial data suggested an up to 97% 28-day mortality rate for intubated COVID-19 patients.[38] After the first wave, some initial registry data were encouraging: mortality for COVID-19 patients on VV ECMO was less than 40%, which was in line with prepandemic outcomes.[32] However, much of that initial enthusiasm has been since tempered, as subsequent waves of the pandemic have shown diminishing returns from the application of VV ECMO in this patient population. Registry data revealed a significant increase in mortality as the pandemic has progressed: after May 2020, mortality for this cohort rose above 50%.[39] Although the underlying reasons for this decline remain somewhat unclear, the available evidence does suggest some possible etiologies.

As the pandemic progressed, more centers with less overall ECMO experience began offering VV ECMO to COVID-19 patients. Registry data did show that hospitals with less ECMO experience witnessed higher mortality rates than more experienced ECMO centers,[39] potentially underscoring the challenges of expanding a complex technology to centers with less volume or training. A recent observational study showed an increased risk of mortality for patients cannulated at a nonspecialized center.[40] In addition, improved medical management of COVID-19 patients, including the use of systemic steroids and antiviral agents together with improved noninvasive oxygenation and ventilation strategies,[41–43] may have led to a sicker, “nonresponder” phenotype of patients being referred for VV ECMO. Although previous VV ECMO studies for ARDS patients had clear inclusion criteria—including, for example, less than 7 days of invasive ventilation[36]—the COVID-19 pandemic challenged these norms. As more patients languished on noninvasive ventilation for weeks before intubation, identifying a cohort of patients who would benefit from VV ECMO has become increasingly challenging. Although avoiding ventilator-induced lung injury is a well-known concept in modern ARDS management and remains the ultimate goal of the “lung rest” afforded by VV ECMO,[44] non–ventilator-associated barotrauma and patient-induced lung injury are not as

clearly defined and are ongoing areas of research.[45] Although some treatment strategies may decrease the number of COVID-19 patients who progress to severe ARDS, there is a real risk of delaying recognition of the cohort of patients who are actively declining with respect to their respiratory disease and are within the window to benefit from VV ECMO. Patients who presented with evidence of barotrauma before intubation, for example, posed challenges to ECMO teams—would these patients receive any benefit from the "lung rest" of VV ECMO?—, and many centers adopted more restrictive VV ECMO inclusion criteria for COVID-19 patients as the pandemic progressed.[40] Some centers applied a more aggressive strategy of earlier VV ECMO cannulation: one small retrospective study showed lower mortality rates with early VV ECMO use, and a significantly lower mortality rate of 25% for patients who were cannulated before intubation.[46]

However, VV ECMO remains a technically challenging and personnel-intensive limited resource, with significant risks associated with its use, and clear guidelines on how and when to apply this technology to COVID-19 patients remain unclear.[47] Unfortunately, most of the data on VV ECMO during COVID-19 comes from retrospective studies, case series, and international registries, which lack control groups or randomization, and are often subject to reporting bias. The heterogeneity between survivors and nonsurvivors of ARDS following COVID-19 is becoming clearer, but the scientific community continues to lack the ability to reliably predict which patients may benefit from VV ECMO and in what manner that technology should be applied. As the body of evidence in this patient population grows, institutions must remain flexible about applying clear inclusion criteria for these patients which reflect best practices for VV ECMO but also take into consideration the resources of the institution or region, as this can significantly impact mortality rates as well.[40] Further studies are needed to focus on defining and identifying severe ARDS phenotypes to better assess the efficacy of such a resource-intensive technology as VV ECMO.

SUMMARY

The COVID-19 pandemic has significantly impacted almost all aspects of modern health care, including increased mortality rates for classically described disease processes. For patients with underlying cardiac disease, concomitant COVID-19 infection significantly increases morbidity and mortality and may precipitate conditions such as CS. Although randomized controlled data are sorely lacking, retrospective evidence shows that patients with COVID-19 and CS are sicker and are more likely to die compared with traditional controls. Similarly, COVID-19 patients with isolated respiratory failure and ARDS seem to have increased challenges compared with historical outcomes. The application of MCS to this patient population remains technically complex and resource intensive, carrying with it a significant mortality rate. Although the scientific community awaits more evidence-based practice guidelines for MCS for COVID-19 patients, the necessity of a thoughtful, multidisciplinary team approach to these challenging cases at high-volume, experienced centers remains of the utmost importance.

DISCLOSURE

All authors have nothing to disclose.

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