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Cardiovascular Collapse in COVID-19 Infection: The Role of Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)

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ABSTRACT (250 words)

COVID-19 has been associated with cardiovascular complications including acute cardiac injury, heart failure and cardiogenic shock. The role of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in the event of COVID-19-associated cardiovascular collapse has not yet been established. We reviewed existing literature surrounding the role of VA-ECMO in the treatment of coronavirus-related cardiovascular collapse. COVID-19 is associated with higher incidence of cardiovascular complications compared to previous coronavirus outbreaks (SARS-CoV, MERS-CoV). We found only one case report from China where COVID-19-associated fulminant myocarditis and cardiogenic shock (CS) was successfully rescued using VA-ECMO as a bridge to recovery (BTR). We identified potential clinical scenarios (cardiac injury, myocardial infarction with and without obstructive coronary artery disease, viral myocarditis, and decompensated heart failure) leading to CS and risk factors for poor/uncertain benefit (age, sepsis, mixed/predominantly vasodilatory shock, prothrombotic state and/or coagulopathy, severe acute respiratory distress syndrome, multi-organ failure or high-risk prognostic scores) specific to using VA-ECMO as BTR in COVID-19 infection. Additional considerations and proposed recommendations specific to the COVID-19 pandemic were formulated with guidance from published data and expert consensus. A small subset of patients with cardiovascular complications from COVID-19 infection may progress to refractory CS. Accepting that resource scarcity may be the overwhelming concern for healthcare systems during this pandemic, VA-ECMO can be considered in highly selected cases of refractory CS and echocardiographic evidence of biventricular failure. The decision to initiate this therapy should take into consideration availability of resources, perceived benefit as well as risks of transmitting disease.

Brief summary (≤60 words):

A significant proportion of patients with confirmed COVID-19 infection experience cardiovascular complications. VA-ECMO can be considered in highly selected cases of refractory cardiogenic shock and echocardiographic evidence of biventricular failure. The decision to initiate this therapy should take into consideration availability of resources, perceived benefit as well as risks of transmitting disease.

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The authors do not have any relevant conflicts of interest to disclose.

The unprecedented global spread of the Coronavirus Disease 2019 (COVID-19) pandemic has resulted in escalating impact on morbidity and mortality across the world, as well as substantial policy change and strain on existing healthcare infrastructure. Although these figures have not yet been firmly established, a recently published systematic review and meta-analysis of 19 observational studies of 2874 patients with confirmed COVID-19 infection showed a pooled prevalence of intensive care unit (ICU) admission of 20.3%, shock (unspecified) in 6.2% and a case fatality rate of 13.9% for infected patients (1). Amidst our present struggles to contain the spread of infection and develop a vaccine, researchers have yet to identify beneficial treatments/therapies in managing patients afflicted with COVID-19 infection.

The COVID-19 pandemic has also uncovered very salient issues in bioethics including stewardship of scarce resources and provision of care to those most likely to benefit from it. Such dilemmas have already been faced by physicians in Italy who have described "warlike" situations in hospitals (2,3). Extracorporeal membrane oxygenation (ECMO) is a resource-intensive form of both respiratory and mechanical circulatory support in the setting of refractory respiratory failure and/or cardiogenic shock (CS), respectively (4). It requires specialized equipment, training (of physicians, nursing staff and perfusionists) as well as delivery of care in specialized critical care units. Despite very poor survival of patients referred for veno-venous (VV) ECMO, interim recommendations from the Chinese (5,6), World Health Organization (WHO) (7) and the Surviving Sepsis Campaign (8) suggest referral for VV-ECMO in cases of COVID-19 pneumonia and refractory hypoxemia despite conventional therapies (9,10).

As COVID-19 has been associated with a multitude of cardiovascular complications (11–13), the role of veno-arterial (VA) ECMO in the event of COVID-19-associated cardiovascular collapse has not yet been established. We sought to review the existing evidence surrounding the role of VA-ECMO in the treatment of coronavirus-related cardiovascular collapse, in an effort to provide some guidance to providers in the face of the COVID-19 pandemic.

Cardiovascular compromise in COVID-19 infection

Compared to other major coronavirus outbreaks such as Severe Acute Respiratory Syndrome (SARS-CoV) and the Middle East Respiratory Syndrome (MERS-CoV), COVID-19 has been associated with increased incidence of cardiovascular complications (11). In one large cohort study of 138 patients, a significant proportion of patients presented with shock (unspecified; 8.7%), acute cardiac injury (7.2%) and arrhythmias (16.7%), while 4 of 138 patients received unspecified ECMO support (14). Various case series have also reported new-onset heart failure/cardiomyopathy as a complication in up to one-third of critically ill patients admitted with COVID-19 infection (9,15). ST-segment elevation in COVID-19-associated myopericarditis has also led to false activations of the cardiac catheterization laboratory (16). Furthermore, among hospitalized patients, the presence of cardiac injury (defined as cardiac troponin above the 99^{th}-percentile upper reference limit) has been independently associated with a four-fold increased risk of mortality in patients infected with COVID-19 (17), with even poorer prognosis in patients who have underlying cardiovascular disease (18). The mechanism(s) by which COVID-19 affects the cardiovascular system remain poorly understood but postulated mechanisms include direct myocardial injury, indirect injury through cytokine release, a prothrombotic state causing microvascular thrombosis, and exacerbation of underlying cardiovascular disease e.g. plaque rupture in susceptible patients (11–13).

We identified two cases from China where COVID-19-associated fulminant myocarditis and CS was successfully treated (19,20). In both cases, the diagnosis of COVID-19 was confirmed by sputum nucleic acid testing. Both patients had markedly elevated cardiac biomarkers (troponin I/T, NT pro-BNP) and depressed left ventricular ejection fraction by transthoracic echocardiography and were treated with empiric broad-spectrum antimicrobials, intravenous immunoglobulin and corticosteroids. In one of these patients, mechanical circulatory support in the form of VA-ECMO was used as a bridge to recovery (BTR) with successful hemodynamic and biochemical improvement (20). Moreover, myopericarditis with left ventricular dysfunction require inotropic support has been reported in the absence of significant pulmonary manifestations (16).

VA-ECMO and COVID-19

The Extracorporeal Life Support Organization (ELSO) recommends consideration of VA-ECMO in refractory CS that persists despite adequate fluid resuscitation, inotropes and vasopressor support (21)**.** Contraindications to VA-ECMO include (but are not limited to) advanced age, life-threatening non-compliance and significant medical co-morbidities (e.g. severe emphysema or cirrhosis) (21). To our knowledge, there are no reported case series' related to the use of VA-ECMO in prior coronavirus outbreaks including SARS-CoV and MERS-CoV**.** Accordingly, we anticipate that patient selection for VA-ECMO in the setting of COVID-19 infection will be a challenging task. However, identification of potential clinical scenarios leading to CS and circumstances unique to COVID-19 may facilitate decision-making (**Table 1**), ideally by a multidisciplinary CS team that includes representation of cardiac surgery, cardiology, intensive care, anesthesia, as well as advanced heart failure/transplant physicians.

Unique clinical features of COVID-19 need to be recognized before considering candidacy for VA-ECMO cannulation in patients with circulatory collapse (**Table 2)**. Age is an independent predictor of mortality among VA-ECMO patients (4), and in a multivariable analysis of COVID-19 patients by Zhou et al. was associated with approximately 10% increased risk of death per year (9). It is of utmost importance to document the presence of both biventricular dysfunction and a hemodynamic profile compatible with CS, as patients with mixed or predominantly vasodilatory shock may be unlikely to benefit from mechanical circulatory support even in the presence of known cardiovascular disease. Although patients with COVID-19 infection are in a pro-inflammatory and prothrombotic state, coagulopathy has been reported in up to one-fifth of cases (9). Hence, vigilant monitoring for both thrombotic complications (intracardiac thrombi, aortic root/aortic valve thrombi, cannula thrombi, thrombosis of oxygenator) and bleeding may be warranted. Lastly, severe cases of COVID-19 tend to present with multi-organ failure. The use of VA-ECMO in such patients, especially in the presence of severe acute respiratory distress syndrome complicated by sepsis, may be considered a futile resource-intensive endeavor. Use of validated prognostic scores such as the Sequential Organ Failure Assessment (SOFA) and Survival after Veno-arterial ECMO (SAVE) scores together with clinical judgment should be encouraged to identify those who are more likely to have an exit strategy, such as BTR (22). The use of VA-ECMO during cardiac arrest is beyond the scope of this review. Reported poor outcomes, however, need to be considered before endeavoring to use this approach. We identified one case where a 79-year female patient with COVID-19 infection was emergently cannulated for VA-ECMO during cardiac arrest and cardiopulmonary resuscitation (E-CPR) but unfortunately this patient died shortly afterward (6).

Based on correspondence from existing societal bodies (7,23,24) and lessons from the experience in China (5,6), we have distilled the major considerations and recommendations for VA-ECMO specific to COVID-19 in **Table 3.** As international experts have written extensively on the major infrastructure changes needed to support COVID-19 patients with VV-ECMO during this pandemic (25,26), we expect that much of this will also apply to patients being considered for VA-ECMO in the setting of refractory CS.

The ethical circumstances surrounding allocation of scarce resources during a pandemic tend to favor a utilitarian approach to maximize collective benefit. Important ethical considerations are outlined in the recently published article by Emanuel et al. with additional recommendations to prioritize certain groups when constrained by limited resources: Health care workers, sickest first, and youngest first (27). ELSO has published guidance (23) surrounding use of ECMO during this pandemic that align with these principles – namely, that the highest priority should be given to younger patients, those with minor/no medical co-morbidities and healthcare workers. Outside of this, standard ECMO inclusion/exclusion criteria and COVID-19 protective equipment should be used according to local institutional policies, as there are currently no special precautions recommended for contact (23). Although there is a theoretical risk of microbial aerosolization in the ECMO membrane oxygenator, this has not yet been substantiated by evidence (28) and we do not recommend any special precautions other than vigilant decontamination and disposal of equipment as governed by local institution and infection control policies.

Pertaining to the provision of ECMO, this is dependent on local institution and regional policies and providing this level of care should be considered dynamically on a case-by-case basis as the local situation and resource availability changes (critical care beds, healthcare personnel, equipment, etc.). In peripheral centers where ECMO is not readily available, additional considerations including ensuring fair resource allocation, as well as the decision to transfer to a specialized center versus cannulation on-site should be determined by similar principles.

At our centre (University Health Network, Toronto) ECMO is considered on a case-by-case basis using an interdisciplinary heart team approach in accordance with the most up-to-date ELSO and Canadian Cardiovascular Society recommendations. To date, we have not yet had any cases of COVID-19 that have required consideration for VV or VA-ECMO. That said, this is an evolving situation that may change as more affected patients are expected to require critical care beds in the coming weeks to months. In our current circumstances worldwide – as MacLaren et al. suggest – resources may well be better concentrated to ensure that enough ICU beds, ventilators and personal protective equipment are available to deal with the influx of patients encountered within the coming weeks to months. As the authors aptly assert, “ECMO is not a therapy to be rushed to the frontline when all resources are stretched in a pandemic” (26).

Conclusions

COVID-19 has the potential to cause significant cardiovascular compromise warranting consideration for advanced therapies in a small subset of affected patients. Frontline providers of all specialties must stay up-to-date with the ever-evolving literature and be familiar with therapeutic options for COVID-19 infections. VV and VA-ECMO remain a resource-intensive form of respiratory and mechanical circulatory support that can be considered in extreme circumstances. In the present time of global uncertainty with limited evidence to guide care, we must be mindful of balancing resource scarcity (which may be the overwhelming concern for many healthcare systems in the course of this pandemic) with perceived likelihood of benefit as well as the risk of transmission to other patients, healthcare providers and patient-care environments. We anticipate that ECMO-CARD (Extracorporeal Membrane Oxygenation for 2019 Novel Coronavirus Acute Respiratory Disease) – an ongoing multicenter prospective observational study of ECMO use in COVID-19 – will inform practice for both VV and VA-ECMO use when it is published (29). For now, it seems reasonable to reserve VA-ECMO for highly selected cases of COVID-19 in refractory CS with echocardiographic evidence of reduced biventricular function, where there is a perceived reasonable probability of benefit as BTR. Discussions around provision of therapy should be made on a case-by-case basis as part of an advanced CS team which involves input from cardiac surgery, cardiology, intensivists, as well as advanced heart failure/transplant physicians to guide appropriate use of this potentially life-saving therapy.

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Table 1: Disease specific clinical scenarios that may lead to cardiogenic shock in COVID-19 infection (**COVID**).

Clinical Scenario	**Comments**
Cardiac injury	Cardiac injury is defined by troponin elevation and can encompass direct myocardial insult or indirect injury due to sepsis, hypoxia, and/or cytokine release. Left ventricular dysfunction and ventricular arrhythmias may be present.
Myocardial infarction in the absence of **O**bstructive coronary artery disease	May result from supply/demand mismatch (Type 2 MI) or from microvascular thrombosis.
Viral myocarditis	Fulminant myocarditis can lead to rapidly progressive CS.
Acute myocardial **I**nfarction	Plaque rupture resulting in STEMI/NSTEMI can be exacerbated due to underlying prothrombotic/pro-inflammatory state.
Acute **D**ecompensated Heart Failure	Can result from decompensation in patients with known or subclinical cardiomyopathy, or from a new process (e.g. Takotsubo/stress cardiomyopathy, septic cardiomyopathy, right ventricular dysfunction)
Abbreviations: MI: myocardial infarction; CS: cardiogenic shock; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction	

Table 2: Risk factors for poor/uncertain benefit from VA-ECMO as bridge to recovery in COVID-19 infection.

Risk Factor
Older age
Sepsis
Mixed or predominantly vasodilatory shock
Prothrombotic state and/or coagulopathy
Concomitant severe ARDS
Multi-organ failure
High-risk prognostic score (SOFA, SAVE)
Abbreviations: VA-ECMO: Veno-arterial extracorporeal membrane oxygenation; ARDS: Acute respiratory distress syndrome; SOFA: Sequential Organ Failure Assessment; SAVE: Survival after Veno-arterial ECMO

Category	**Recommendations**
Ethical considerations for resource allocation	ECMO should only be provided if institutional resource constraints allow for it. The following groups should be given priority: ✓ Sickest first ✓ Youngest first ✓ Greatest perceived benefit ✓ Fewest co-morbidities ✓ Healthcare workers
Patient selection	Determined by standardized (ELSO, CCS, WHO) and institutional

timing, and management	protocols. At present, this includes: ✓ Case-by-case discussion with interdisciplinary heart team ✓ Usual patient selection criteria as for non COVID-19 patients ✓ Standard administration, monitoring (e.g. POCUS, hematologic parameters) and management of complications ✓ Standard adjunctive therapies (e.g. lung protective ventilation, CRRT) Patients referred for consideration of VA-ECMO from peripheral centres should be discussed on a case-by-case basis (including the decision to transfer to a specialized center vs. cannulate on-site).
Environmental and infection control precautions	Determined by standard institutional protocols: At present, this includes: ✓ Patients on ECMO should be in negative pressure isolation rooms when possible ✓ N95 masks for aerosol-generating medical procedures only ✓ Droplet-contact precautions otherwise including during cannulation and/or routine rounding
Handling of ECMO equipment	All ECMO equipment should be used and disposed of according to local institutional and infection control policies with attention to practicing strict decontamination.
VA-ECMO During E-CPR	E-CPR should only be performed at experienced institutions (depending on local policy, perceived risk-to-benefit ratio and availability of resources) as the uncontrolled environment of cardiac arrest can pose significant risk of cross-contamination and transmitting infection.
Abbreviations: VA-ECMO: Veno-arterial extracorporeal membrane oxygenation; ELSO: Extracorporeal Life Support Organization; CCS: Canadian Cardiovascular Society; WHO: World Health Organization; POCUS: Point-of-care ultrasound; CRRT: Continuous renal replacement therapy; E-CPR: Extracorporeal membrane oxygenation during CPR	

Table 3: Additional considerations and proposed recommendations for VA-ECMO during the COVID-19 pandemic

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