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**In-depth review of cardiopulmonary support in COVID-19 patients with heart failure**

Raffaello WM *et al*. Cardiopulmonary support and HF in COVID-19

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**Abstract**

Coronavirus disease 2019 infection has spread worldwide and causing massive burden to our healthcare system. Recent studies show multiorgan involvement during infection, with direct insult to the heart. Worsening of the heart function serves as a predictor of an adverse outcome. This finding raises a particular concern in high risk population, such as those with history of preexisting heart failure with or without implantable device. Lower baseline and different clinical characteristic might raise some challenge in managing either exacerbation or new onset heart failure that might occur as a consequence of the infection. A close look of the inflammatory markers gives an invaluable clue in managing this condition. Rapid deterioration might occur anytime in this setting and the need of cardiopulmonary support seems inevitable. However, the use of cardiopulmonary support in this patient is not without risk. Severe inflammatory response triggered by the infection in combination with the preexisting condition of the worsening heart and implantable device might cause a hypercoagulability state that should not be overlooked. Moreover, careful selection and consideration have to be met before selecting cardiopulmonary support as a last resort due to limited resource and personnel. By knowing the nature of the disease, the interaction between the inflammatory response and different baseline profile in heart failure patient might help clinician to salvage and preserve the remaining function of the heart.

**Key Words:** COVID-19; Heart failure; Cardiopulmonary support; Extracorporeal membranous oxygenation; Ventricular assist device; Coagulopathy

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**Core Tip:** Coronavirus disease 2019 (COVID-19) infection might cause severe respiratory distress and demonstrates an extrapulmonary involvement. Recent evidence shows direct involvement of COVID-19 and deterioration of the heart function. Severe infection is commonly found in high risk population, indicates a complex interaction between host inflammatory response and the infection itself, signifies the use of cardiopulmonary support and associated with high mortality. There are relatively scarce information regarding the use of ventricular assist device and extracorporeal membrane oxygenation and here we will be discussing the possible mechanism of how cardiopulmonary support may improve COVID-19 infection outcome.

**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) is an emerging viral infection which has caused global pandemic with resulting both high global economic burden and mortality rate[1,2]. It also caused an alteration and restructuration in our healthcare system, especially in treating patients with infection and chronic disease[3]. Patients with both condition of COVID-19 and prior cardiovascular disease have an increased risk of cardiovascular complications which severely affect the mortality rate.

COVID-19 is also associated with higher incidence of cardiovascular complication in compare to previous coronavirus outbreaks[4,5]. Deterioration of the cardiac function is prominent in COVID-19 and those with lower baseline function are prone to further decline in cardiac function. A study demonstrate the preexistence of chronic heart failure (CHF) and high cardiac biomarkers is associated with worse outcome[6]. Recent study also shows that patient with heart failure (HF) is associated with an increased risk of mechanical ventilation and overall mortality regardless of left ventricular ejection fraction (LVEF)[7].

The use of cardiopulmonary support in COVID-19 shares the same prominent role in managing severe conditions such as severe respiratory distress and heart failure[3,8]. However, there are several distinct clinical characteristics of HF patients which may differ from non-pre-existing HF patients. These factors have to be considered before choosing cardiopulmonary support as a treatment of choice. Another challenging issue is the highly selective inclusion and exclusion criteria before a patient is eligible for the use of extracorporeal membranous oxygenation (ECMO). Therefore, the management of both HF and COVID-19 has to be tailored since the concept of one treatment fits all might not suitable in these patients.

**HEART FAILURE AND COVID-19**

The mechanism of cardiac function disturbance in COVID-19 is poorly understood and it is thought to be an interaction between several mechanisms including direct myocardial injury, cytokine release, prothrombotic state causing microvascular thrombosis and exacerbation of underlying cardiovascular disease[3,9–13]. In the context of COVID-19, CHF patients are vulnerable to acute exacerbation. These patients are at risk because of their lower baseline status which unable to cope with the increasing metabolic demand in systemic inflammation triggered by the infection[14]. In the settings of advanced HF with left ventricular assisted device (LVAD) support, functional capacity of the lung has already impaired and contributes even more to the decrease of the cardiopulmonary reserve[15,16].

Several studies have demonstrated more severe infections and higher mortality rate in patients with preexisting cardiovascular disease[6,7,14,17]. Older age along with other comorbid such as obesity, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, atrial fibrillation, chronic kidney disease and frailty are seems to be more prevalent in the HF group and might contribute to an increased rate of mortality and morbidity[7,18]. Moreover, these patients generally have a reduced immunity, general frailty, an tend to be in an inflammatory state[14,19].

A lower pulmonary function is commonly found in HF patients and is contributed mainly by chronic obstructive pulmonary disease (COPD)[20]. Combination of underlying parenchymal disease and elevated left ventricular filling pressure leads to the development of pulmonary hypertension[21]. In COVID-19 infection, respiratory failure and acute respiratory distress syndrome (ARDS) further exacerbates pulmonary vasoconstriction and interstitial edema. This condition is further worsened by pre-existing biventricular failure and ARDS that eventually lead to right ventricular function impairment.

Recent studies have shown that COVID-19 is associated with acute myocardial involvement which described as an acute cardiac injury[3,12,13]. A suspicion of cardiac involvement in COVID-19 is best described by an elevation in cardiac biomarker [high-sensitivity troponin (hs-TnI)] above 99th percentile upper reference limit[13,22]. Early reports had been analyzed, with notable findings suggest an increased level of cardiac troponin was associated with admission to intensive care and higher in hospital mortality[12,23–26]. A careful observation of endomyocardial biopsy in COVID-19 patients has revealed an evidence of acute myocardial inflammation through the presence of viral particles and a diffuse myocardial edema on cardiac magnetic resonance, therefore raising the suspicion of direct viral myocardial invasion[27]. Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV2) binds with angiotensin-converting enzyme 2 (ACE2) receptor and with the help of transmembrane protease serine 2 (TMPRSS2), facilitates viral entry through the cell[28,29]. ACE2 and TMPRSS2 are widely expressed in various tissue, including the heart, and might explain the involvement of heart during the course of infection[29]. Viral inclusion bodies were found from the biopsy of myocardial tissue along with identification of SARS-CoV2 genomic RNA  in patients with suspected COVID-19 myocarditis, therefore raising the possibility of direct viral invasion to the myocardium[30–33]. Although there was a high viral load which is associated with higher proinflammatory cytokine expression in the cardiac tissue, these findings were not accompanied with an elevated inflammatory cell infiltrates[34]. The exact proportion of myocarditis is still hard to be determined, mainly because of the lack of definitive diagnostic procedure done in the patients[13,27]. However, myocarditis is important to be considered as it may cause abnormal electrical conductance in the myocardium[10].

Myocardial infarction plays a significant role in the development of acute HF in COVID-19 infection. Both Type I and II myocardial infarction might occur in patient with COVID-19, worsening the function in an already impaired baseline function[3]. This may leads to worse outcome in patient with a history of HF[3].

Cardiac arrhythmia is a major concerning issue in the context of HF and COVID-19 infection. Careful observation of the heart rate and rhythm are vitals in the clinical settings. Atrioventricular block, atrial fibrillation, polymorphic ventricular tachycardia and pulseless electrical activity have been closely associated with COVID-19 despite of the unknown mechanism of how these rhythms abnormalities may develop[22,35]. QT prolongation is constantly a thread, considering that QT prolongation is an independent risk factor of adverse outcome in advanced heart failure[36]. Even though the use of hydroxychloroquine and azithromycin is no longer recommended due to the lack of evidence to reduce mortality and severity, patients with HF are often already have underlying structural abnormalities. These abnormalities are related to the delay of ventricular repolarization which is manifested on electrocardiogram (ECG) as prolonged QT interval[37–39]. The use of another agents such as loop diuretic, may promote electrolyte imbalance and increase the risk of developing malignant arrhythmia. Sepsis is a known risk factor for QT prolongation that has to be considered in these patients[40]. The proposed mechanism of cardiac function deterioration is depicted in Figure 1.

**ROLE OF INFLAMMATORY RESPONSE IN HEART FAILURE PATIENTS WITH COVID-19**

Profound cytokine release in the setting of severe COVID-19 infection is commonly found. The release of proinflammatory cytokines, increased metabolic demand and coagulation disorder in sepsis may contribute to the development of new onset HF and decompensation episodes in CHF[41]. Cytokine storm is observed in viral induced infection such as influenzae and COVID-19 and in the setting of graft-versus-host disease. Lymphopenia, C-reactive protein, lactate dehydrogenase, ferritin, D-dimer and troponin are among the biomarkers that reflect the severity of the hyperinflammatory state[42,43]. In HF, the inflammation happened as a response to the myocardial stressors. Multiple preexisting comorbidities that might further contribute to the profound inflammatory response are coronary artery disease, hypertension, arrhythmia, diabetes, and obesity. Increased level of inflammatory cytokine directly linked to the deterioration of the heart function[44,45]. The increased level of several cytokines such as tumor necrosis-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and galectin-3 may predict worse outcome in HF patients[46,47]. Interestingly, an elevation of IL-6 Level is also seems to be correlated with mortality in COVID-19 infection[48]. Moreover, the systemic hyperinflammation state that might occur in the setting of COVID-19 has extrapulmonary involvement and causing additional burden to the heart. The effect of hyperinflammation is well reflected by an elevation of cardiac biomarkers such as troponin and N-terminal pro B-type natriuretic peptide[43]. In this stage, vasoplegia and myocarditis might also occur[43].

Pro-inflammatory response which is induced by the infection might worsen hypoxia which in turn causing more stress to the damaged heart[42]. Hypoxia serves as a risk factor of survival in COVID-19 patients and should not be overlooked since it has deleterious effect in patients with HF and COVID-19[49]. Acute respiratory distress syndrome and exaggerated inflammatory response contributes to the development of hypoxia which may cause cardiac lesion and further exacerbates HF[50–53].

**COAGULOPATHY IN THE WORSENING HEART DURING COVID-19**

Coagulopathy is a common disorder found in COVID-19 infection. It is thought that the interaction between host defense mechanism and coagulation system during COVID-19 infection may lead to hypercoagulability and a high prevalence of thrombotic events[54–56]. This finding is reinforced by an elevated D-dimer level which is often present in the setting of COVID-19 infection[5,55]. The combination of endothelial dysfunction, inflammatory state, oxidative stress and platelet activation are thought to be responsible for a hypercoagulable state[1,5,55]. The true nature of the course is remain unknown to date, however the role of endothelial activation cannot be overlooked. It is thought that ACE2 receptor that serves as an entry point for the SARS-CoV-2 into the cell, plays an important role[57,58]. The presence of ACE2 receptors on the endothelial cells as well as antithrombin (AT), heparin and other anticoagulation might play an important role in regulating the inflammatory response[57]. AT interacts with heparin-like glycosaminoglycan (GAG) on endothelial surface and therefore involved in the release of prostacyclin which will inhibit leukocyte activation by decreasing IL-6 Level[57,59]. The hypercoagulability state is also involved in the development of both micro- and macrovascular thrombus and may also plugs the extracorporeal circuits[5,55]. Grave consequence of thrombosis may occur in COVID-19 patients as it may present as pulmonary venous thrombosis leading to right heart failure and or microvascular thrombosis may leads to myocardial dysfunction, worsening the heart function[5,55,60–62].

Patients with a preexisting history of heart failure are already in an increased risk for developing thromboembolism due to venous stasis, endothelial injury, ischemic cardiomyopathy and atrial fibrosis[63,64]. This condition might be worsened by the presence of COVID-19 infection which may trigger coagulopathy and the presence of implantable device which also may trigger thrombosis[65,66]. The pre-existing cardiopulmonary support such as left ventricular assisted device (LVAD) alone might increase the risk of developing pump thrombosis, although the risk of stroke with co-existing COVID-19 infection has not been assessed yet[3,67].

**CARDIOPULMONARY SUPPORT IN COVID-19 PATIENTS WITH HEART FAILURE**

Patient with COVID-19 might require mechanical circulatory support as a consequence of COVID-19 induced cytokine release syndrome or cytokine storm[3]. Hypoxemic respiratory failure may cause circulatory collapse in a small subset of patients and the need of lung-protective ventilation (LPV) in these patients is evident[68,69]. The use of extracorporeal life supports (ECLS) is reserved for patients with refractory hypoxemia or hypercarbia, right ventricular failure as a consequence of hypercarbia and acidemia, and hypoxic pulmonary vasoconstriction. These patients might have benefit from the use of venovenous (V-V) ECMO while those who suffer from refractory cardiogenic shock might consider the use of venoarterial (V-A) ECMO which might improve cardiac condition by pronounced LV unloading[70–72].

However, the use of these devices is remain in question since significant resources such as specialized equipment and trained personnel are needed to plant and maintain the device[4,42]. The decision of implanting the device might be considered for patients with ARDS and or cardiogenic shock refractory to traditional management with favorable outcome with the use of the device[68]. Close monitoring is also essential and health care workers exposure is also needed to be looked closely[42]. Still, despite the use of cardiopulmonary support, management of patients with HF and COVID-19 infection remain difficult due to complex interaction between the volume status and the biventricular dynamics[42]. There are also strict criterias have to be met before implanting ECMO in COVID-19 patient. While there are no difference for indication of ECMO between COVID-19 and non-COVID-19 patient, there are several things to be remembered[68]. First, careful selection is needed as patients with advanced age and significant comorbidities might not have much benefit from the use of ECMO. Also, patient with underlying CHF tend to be older, have multiple existing comorbidities and often fall into profound clinical status in the natural course of COVID-19 infection[6,7,14]. Therefore, the use of ECMO should be restricted in these patients unless there are a reasonable chance of recovery[5]. The use of ECMO should be carefully taken, considering that the hospital capacities and resources are limited in most settings and the possible outcome that the patient might achieve[5,42,68].

There are some small subset of patient who may choose another options in regard to  the treatment of advanced HF. Patients who are not eligible for the heart transplant might use the left ventricular assist device (LVAD). However, the use of this device is not without risk, especially in the context of COVID-19 infection. These patients are known to have different types of HF that may produce different inflammatory profile in response to the implanted device[47]. To the best of our knowledge, until now there are no specific indication of when to implant ventricular assist device (VAD) in the context of severe COVID-19. First reported case of VAD implantation in patient with COVID-19 infection demonstrate the possibility of VAD as an alternative in a setting of prolonged cardiogenic shock and hemodynamical instability with modest chance of VA ECMO weaning[65]. Careful consideration and assessment of patient’s clinical status has to be put in top priority in determining when to implant the device. The indications and contraindications for ECMO in COVID-19 is described in Table 1.

The presence of hardware in the body and prolonged support such as LVAD may cause immune dysregulation, increase the risk of infection and cellular immunity impairment as prior studies had already demonstrated[47,66,73,74]. In COVID-19, severe inflammatory response might induce profound patient’s clinical status and worse outcome. The pre-existing LVAD in severe COVID-19 infection may raise some concerns in the context of management. The risk of pump thrombosis has to be kept in mind, as hypercoagulability state in COVID-19 infection and the pump itself may induce thrombosis[65]. Despite of severe hypoxemia might improve by prone position, there is a specific concern of the outflow graft compression, driveline damage and elevated pressure in the right ventricle with subsequent right ventricular failure[66,67]. Moreover, additional load to the right ventricle may predispose to right heart failure which is well known as a potential etiology of hypotension in the setting of LVAD use and inflammatory surge[66,67]. However, prone position in patients with LVADs is not contraindicated in the management of hypoxemic respiratory failure although more data are needed[3].

Anticoagulant use in LVAD patient has to be closely monitored  due to a high risk of thrombosis in this population[3,14]. More interestingly, patient with COVID-19 infection may often shows a hypercoagulability state despite therapeutic dose of anticoagulation and to overcome this state, requires an increase dose which will carry the risk of life-threatening bleeding[75]. Still, thromboembolism carries a significant risk of adverse outcome and the use of closely monitored anticoagulation might have a beneficial role[55].

Several biomarkers that reflect the severity of hyperinflammation in COVID-19 might be obtained before the infection and serves as a baseline markers in patient with LVAD. Baseline lactate dehydrogenase (LDH), absolute lymphocyte count, troponin and  natriuretic peptide that are taken prior the infection might bring an important information that should not be overlooked[42]. These indicators are valuable in following LVAD patients with COVID-19 infection[42]. The role of cardiopulmonary support in COVID-19 infection is illustrated in Figure 2.

**CONCLUSION**

As discussed above, COVID-19 infection has deleterious effect on the heart function. In addition, exaggerated inflammatory response in severe COVID-19 infection in combination with preexisting impairment of the heart function and multiple comorbid as seen in the HF patients may severely affect the outcome. Cardiac function in patient with HF should not be overlooked as deterioration of the heart function may occur rapidly as a consequence of the infection. Therefore prompt diagnosis and early monitoring of the heart function are critical in the management. Careful monitoring of inflammatory marker during the course of the disease might also play an important role, as patient with advanced HF often have their baseline checked regularly. Any elevation of the inflammatory marker might serve as a clue of worsening inflammation and the heart function.

Another thing needs to be considered is the use of anticoagulation in severe COVID-19 patients with heart failure might have beneficial effect. Hypercoagulability state is often found in the patient, it is possibly because of the inflammatory response and the implanted device that may induce coagulation. However the risk of bleeding has to be kept in mind since fluctuant international normalized ratio and overt bleeding is not uncommon[55,76–78].

The use of cardiopulmonary support in this patient remains an issue. A small subset of patients with implanted LVAD also need to be concerned as unfamiliarity of the healthcare personnel to the device and the possible manipulation of the patient’s position such as prone position might increase the right ventricular pressure and might lead to hypotension[66]. The use of ECMO and COVID-19 is very challenging due to its highly selective criteria and contraindicated in most patient with COVID-19 due to multiorgan dysfunction, significant comorbidities and the risk of bleeding[5,8].

Currently, supportive treatment remain the mainstay of treatment for COVID-19 infection. Focus is now directed on primary prevention and vaccination program. High burden and mortality rate was found in patient with preexisting cardiovascular disease, therefore American college of cardiology recommends to prioritize vaccination program in this high risk group[79].

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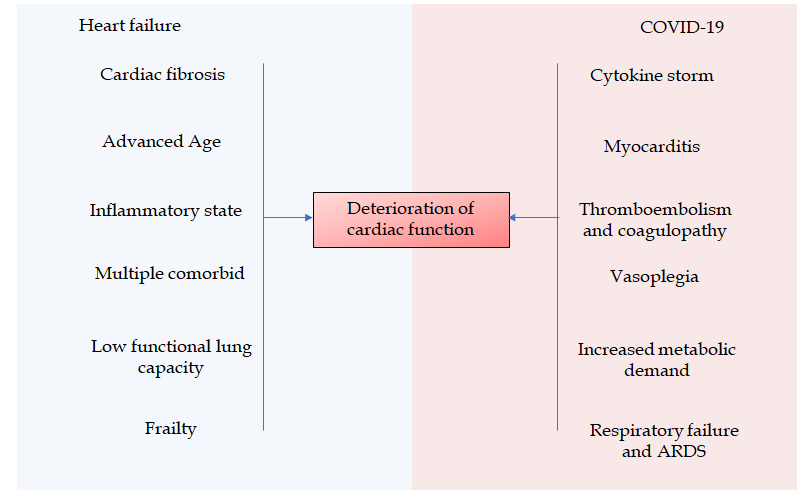
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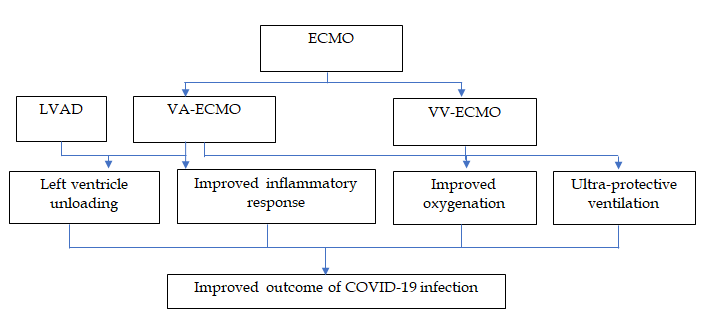
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**Figure Legends**



**Figure 1 Proposed mechanism of deterioration of cardiac function in preexisting** chronic Heart failure **patient with coronavirus disease 2019 infection**. CHF: Chronic Heart failure; COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome.



**Figure 2 Proposed role of cardiopulmonary support in coronavirus disease 2019 infection**. ECMO: Extracorporeal membranous oxygenation; LVAD: Left ventricular assist device; VV: Venovenous; VA: Venoarterial; COVID-19: Coronavirus disease 2019.

**Table 1 Indications and contraindications for Extracorporeal membranous oxygenation in coronavirus disease 2019**

|  |  |
| --- | --- |
| Indications for ECMO | Contraindications for ECMO |
| V-V ECMO   * PaO2/FiO2 < 60 mmHg for > 6 h < 50 mmHg for > 3 h * pH < 7.2 with PaCO2 > 80 mmHg for > 6 h | Relative contraindications   * Age ≥ 65 yr old * Body mass index ≥ 40 * Immunocompromised status * No legal medical decision maker available * Advanced chronic underlying systolic heart failure * High dose vasopressor requirement (and not under consideration for VA or V-VA ECMO)   Absolute contraindications   * Advanced age * Clinical frailty scale category ≥ 3 * Mechanical ventilation > 10 d * Significant comorbidities: * Chronic kidney disease ≥ III * Cirrhosis * Dementia * Baseline neurological disease which might prohibit rehabilitation potential * Disseminated malignancy * Advanced lung disease * Uncontrolled diabetes with chronic end-organ dysfunction * Severe deconditioning * Protein-energy malnutrition * Severe peripheral vascular disease * Other preexisting life-limiting medical condition * Nonambulatory or unable to perform activities * Severe multiple organ failure * Severe acute neurologic injury (example: anoxic, stroke) * Uncontrolled bleeding * Contraindications to anticoagulation * Inability to accept blood products * Ongoing cardiopulmonary resuscitation |
| V-A ECMO   * Refractory cardiogenic shock   + persistent tissue hypoperfusion   + systolic blood pressure < 90 mmhg   + cardiac index < 2.2 L/min/m2 while receiving noradrenaline > 0.5 mcg/kg/min   + dobutamine > 20 mcq/kg/ min or equivalent |

ECMO: Extracorporeal membranous oxygenation; V-V: Veno-venous; V-VA: Veno-Venoarterial; V-A: Veno-arterial.