Multiorgan failure during COVID-19 pandemic in cardiovascular patients. Role of advanced cardiac and pulmonary support

Fallo multiorgánico durante la pandemia de COVID-19 en pacientes cardiovasculares. Rol de la asistencia circulatoria y pulmonar

ABSTRACT

COVID-19 has now claimed several thousands of lives and overwhelmed the healthcare systems of several countries. Patients with cardiovascular disease are at particular risk not just of the infection itself but of its cardiac complications. Compared to other hospitalized patients with COVID-19, those needing intensive care, are more likely to have preexisting cardiovascular diseases or risk factors. Cytokine storm with hyperinflammation correlates with the severity of the disease. It is associated with mortality and is a key factor in determining the clinical course of extrapulmonary multiple-organ failure, suggesting that the inflammatory storm is associated with damage in extrapulmonary tissues and organs. Advanced Cardiac and Pulmonary Support has been reported in selected a COVID population.

Keywords: COVID-19 pandemic, multiorgan failure, cardiovascular patients, advanced cardiac and pulmonary support.

INTRODUCTION

Patients with cardiovascular disease are at particular risk not just of the infection itself but of its cardiac complications. Cytokine storm is associated with mortality and is a key factor in determining the clinical course of extrapulmonary multiple-organ failure. Advanced cardiac and pulmonary support has been applied in selected COVID population.

ILLUSTRATIVE CASE REPORT

A 68-year-old man was hospitalized in Sirio Libanês Hospital (São Paulo, Brazil) after neurosurgical treatment (temporal meningeoma removal). At the 5th post-surgical day he started having fever, hypoxia and respiratory failure requiring mechanical ventilation. Chest CT showed a lesion of right lower lung and diffuse consolidation on both lower lungs. Nasopharyngeal swabs were positive for SARS-CoV-2 (COVID-19) nucleic acid by the fluorescence quantitative RT-PCR. His relevant comorbidities were obesity, hypertension, rheumatoid arthritis, coronary artery disease and prosthetic cancer without metastatic lesion. Blood tests revealed WBC 4.8x10^9/L, LYM 0.10x10^9/L and elevated inflammatory markers as D-dimer, ferritin, troponin, lactate dehydrogenase (LDH) 1052 U/L, procalcitonin (PCT) 0.71 ng/ml, C-reactive protein (CRP) 24 mg/L. Blood gas analysis revealed: pH 7.17, PO2 71 mmHg, pCO2 58 mmHg with fraction of inspired oxygen (FiO2) 100% and the need of high doses of dobutamine (20 mcg/kg/min) and noradrenaline (0.8 mcg/kg/min) due to low mean arterial blood pressure of 50 mmHg. Medical treatment with hydroxychloroquine 400 mg, azithromycin 500 mg and methylprednisolone 40 mg was started together with vancomycin, meropenem, fluconazole as coverage in case of a superimposed infection. All these means did not improve his clinical situation. Due to refractory cardiogenic shock with renal and pulmonary failure, percutaneous peripheral Veno-Arterial extracorporeal membrane oxygenation (V-A-ECMO) support (Maquet) was inserted at bedside. A heparin coated cannula (Maquet) was placed into the left femoral artery with a leg reperfusion cannula, and a heparin coated cannula...
Immune System out of control in COVID-19 heralds multiorgan failure

When SARS-CoV-2 enters a cell to replicate, it can disable or destroy it, leading to the release of potential danger signals to activate the host’s immune response. A rapid and well-coordinated innate immune response is the first line of defense against viral infection. The production of Interferon IFN-I or α/β is the key natural immune response. It is hypothesized that a delayed release of interferons (IFNs) in the early stages of COVID-19 infection that hinders the body’s antiviral response and generate high levels of proinflammatory cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF) and chemokines] through elevated serum cytokine and chemokine levels related to the high number of neutrophils and monocytes in the patients lungs and peripheral blood. Dysregulated and excessive immune responses may cause immune damage to the human body. The virus eliminates key lymphocytes, particularly CD4+ as coordinator of T cell function. The lower the lymphocyte count, the worse the outcome. With the immune system partially disabled, the macrophages and then neutrophils come in as a second line with IL-1 and IL-6 arriving on the scene particularly in the sickest COVID-19 patients where their blood has high levels of these immune system proteins developing the “cytokine storm” picture where the body starts to attack its own cells and tissues rather than just fighting off the virus.  

**Impending storm ahead**

When biomarkers start rising particularly when CRP, troponin, IL-6, ferritin, D-dimer, creatinine start rising means that there is an impending storm. It means that some of these processes are at play and is particularly important given that many patients with CVD have heightened angiotensin-converting enzyme 2 (ACE2) receptor activity to begin with, making them vulnerable to COVID-19. Those who have higher levels of markers should be followed closely, monitored for arrhythmias, ischemia and organ failure particularly in CV patients, with efforts made to restore immune balance. Intervention will likely need to be instituted early, before the immune amplification process is fully underway. This cytokine storm is associated with disease progression in patients with high levels of IL-1B, IL-2R, IL-6 IFN-γ, IP-10 and monocyte chemoattractant protein 1 (MCP-1) and the larger the number of immune cells that results in hyperinflammation correlate with the severity of the disease. In patients with acute respiratory distress syndrome (ARDS) cytokine level increase is positively correlated with mortality rate and is also a key factor in determining the clinical course of extrapolunmonary multiple-organ failure, suggesting that the inflammatory storm is associated with damage in extrapolunmonary tissues and organs. It also might explain why some people have a severe reaction to coronaviruses while others only experience mild symptoms particularly younger people as their immune systems are less developed and so produce lower levels of inflammation-driving cytokines. Systemic inflammation has long been posited as a trigger for cardiovascular events and the body’s potent immune response to COVID-19 poses unique risks to the heart and may result in part from a predilection of COVID-19 for the cardiovascular system, combined with the already widespread prevalence of cardiovascular disease that places patients at high risk of COVID-19 complications. Systemic inflammation has long been posited as a trigger for cardiovascular events and the body’s potent immune response to COVID-19 poses unique risks to the heart and may result in part from a predilection of COVID-19 for the cardiovascular system, combined with the already widespread prevalence of cardiovascular disease that places patients at high risk of COVID-19 complications. Positve feedback between cardiovascular disease and abnormal immune function might explain the increased risk of death in COVID-19 patients with cardiovascular risk factors. Age (especially), diabetes, hypertension and obesity promote immune system dysregulation, while this dysregulation affects cholesterol metabolism and systemic inflammation. Thus elderly patients with cardiovascular disease are especially vulnerable and the presence of cardiovascular risk factors may be a marker of accelerated immunologic aging or dysregulation that increases the likelihood of cardiovascular complications during the infection. The virus uses ACE-2 receptors to get into the cell that are highly expressed in the myocardium in addition to the lung and other organs.
Reports describing fulminant myocarditis confirmed at autopsy by the presence of inflammatory, mononuclear infiltrates, and even the virus itself as shown in an Italian patient with cardiogenic shock23 remind us that the heart, and not just the lung, is a target.3,10. ACE-2 receptors are also present in other organs and systems, including kidneys, eyes, gut, liver, vasculature and central nervous system that might attract inflammatory cytokines and multiorgan failure27. Severe COVID-19 infection can damage the heart through direct viral infection but also due to poor oxygenation, hemodynamic stress, hypercoagulability, exacerbation of diabetes and hypertension5,11. Elevated troponin or CK-MB levels may result from myocardial ischemia or non-ischemic processes such as myocarditis, and it frequently accompanies severe COVID-19 infections. Compared to surviving patients, those who die have significantly higher troponin levels, especially when acute respiratory distress syndrome (ARDS) has complicated the picture10. Cohort studies from hospitalized patients estimate that myocardial injury occurs in 7-28%6,7,29-31 and is significantly more common in admitted intensive care and in those who died1. Even patients without known CV disease can die with elevated troponin levels and cardiac arrest28,32. It is clear that several mechanisms can injure the heart which singly or together can present in different ways (Figure 1), depending upon the pre-existing conditions, viral processes, degree of hypoxia, and inflammatory response of the patient5,23.

Heart failure and cardiogenic shock can develop in COVID-19 patients. The complexity of these cases and their frequent progression to multiorgan dysfunction can often cloud the “exact” cause of death9. Zhou et al. observed heart failure in 23.0% of COVID-19 patients, and in 52% of the non-survivors20. The report from Washington state noted that 33% of intensive care patients developed cardiomyopathy19. The occurrence of pulmonary edema in COVID-19 infections is another source of clinical confusion, that is, whether it is non-cardiogenic (ARDS), cardiogenic, or both. It is important to distinguish these entities when managing the respiratory manifestations of COVID-19. Right heart catheterization has been discouraged, as ICU physician trend to use the Berlin criteria for ARDS46 and volume status can be assessed with serum brain natriuretic peptide levels and cardiac echocardiography35. Still, pulmonary artery catheterization may be considered as different management strategy for ARDS and left heart failure.

Arrhythmia, venous thromboembolism, strokes and skin lesions are also frequent complication in multiorgan failure36-38. The appearance of a new or marked worsening of an existing arrhythmia can result from the metabolic, neurohormonal, and inflammatory stress of COVID-19 infection in patients with or without cardiovascular disease36-39 in particular malignant tachyarrhythmia appear in the setting of elevated troponin or myocarditis40. Most COVID patient may be at risk of arrhythmias caused by medication, electrolyte disorders, or both. Therapy combining hydroxychloroquine plus azithromycin can prolong QT-interval and generate fatal arrhythmias41. A 2000 patients NIH trial is underway to test safety and efficacy of this combination42. Recently a large multinational cohort study showed no benefit mainly due to arrhythmias43. This combination is no longer used in most countries.

The pro-coagulant effects of an overactive inflammatory response can increase the likelihood of thrombosis and embolism44. Abnormal coagulation parameters may be present in severely ill patients with COVID-19 and are associated with increased mortality3,44-46. D-dimer levels are strongly associated with in-hospital death44 along with fibrin degradation product levels with a frequent finding of disseminated intravascular coagulation44-46.

Anticoagulation appears to have a critical role according to recent data47.

**Sequential organ failure assessment score**

The Sequential Organ Failure Assessment (SOFA) score is a mortality prediction score that is based on the degree of dysfunction of six organ systems48-49.

- The score is calculated on admission and every 24 hours until discharge using the worst parameters measured during the prior 24 hours.
- The scores is used in a number of ways.
- As individual scores for each organ to determine progression of organ dysfunction.
- As the sum of scores on one single ICU day.
- As the sum of the worst scores during the ICU stay.

The early detection of multiorgan failure can be an early marker of cytokine storm and mortality prediction or resources use49.

**Targeting therapy during the storm**

On top of the most frequent used medications in COVID-19 patients49-51 dozens of studies have been launched to see whether drugs and devices that block cytokines, or prevent their release in the first place, may keep COVID-19 patients from deteriorating and dying. Many anti-inflammatory agents have already been tested in the prevention of cardiovascular events52. Anti-COVID-19 anti-cytokine storm candidates include tocilizumab (Actemra®; Roche) and sarilumab (Kevzara®; Sanofi/Regeneron), both currently being studied and, could be affective reducing the risk of fatal ventricular tachycardia/fibrillation. Others are anakinra (Kineret®; Sofib); siltuximab (Sylync®; EUSA Pharma) and ruxolitinib (Jafaki®; Incyte). Numerous studies are examining their effects on IL-6 and/or IL-1, key actors in the body’s response to COVID-19 that can alter heart rhythm and drug absorption. Recently, a preliminary report randomized trial with dexamethasone in severe COVID-19 patients RECOVERY Trial showed a significant reduction in mortality in those receiving oxygen or on invasive mechanical ventilation. (Hobry P, Lim WS, Emberger J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv BMJ Yale. The preprint server for health sciences.doi: https://doi.org/10.1101/2020.06.22.20137273).

The medical community has so far proposed over 100 clinical trials in severe inflammatory storm including application of mesenchymal stem cells or haemadsorption.

**Mechanical assist devices and extracorporeal devices in multiorgan failure and shock**

As described earlier, cardiovascular patients are more often affected and compromised by the virus or by the cytokine
storm, meaning that any ARDS needs to be assessed for cardiovascular involvement as heart failure or mixed shock can be confirmed and measured by physiologic parameters and echocardiography. Shock might be an uncommon but life-threatening complication of a COVID-19 infection. Giving the high number of infections however, an incidence of shock in 6.0% of all of COVID-19 patients translates in a significant number of patients [53].

A significant number of hospitalized patients with COVID-19 will develop acute respiratory distress syndrome (ARDS) [54-56]. According to one study, 12% of admitted patients progress to requiring mechanical ventilation with 3% needing extracorporeal membrane oxygenation (ECMO) support [57].

Guidelines should stress the importance of performing all other evidence-based interventions, such as lung-protective ventilation and prone positioning, prior to the consideration of ECMO [58]. ECMO is a tool of cardiopulmonary support for refractory respiratory and cardiac failure. There are 2 main types: veno-venous (V-V) and veno-arterial (V-A). V-V ECMO is used to correct hypoxemia and hypercapnia in isolated lung failure. In one form, a single dual-lumen catheter draws blood from a large vein and reinfuses oxygenated blood back into the right atrium [59]. Another uses 2 cannulas, usually drawing blood from a femoral vein and reinfusing it via the internal jugular vein into the right atrium. Dual-site cannulation is preferred for COVID-19 patients for pulmonary support, as it can be performed safely at the bedside without the need for fluoroscopy or transesophageal echocardiography, so that fewer personnel need to come into the room. V-A-ECMO provides cardiac and circulatory support in addition to oxygenation [60].

Nonrandomized studies, case series, and reports of using ECMO as a bridge to recovery in ARDS during the 2009 influenza A (H1N1) epidemic suggest that the mortality rate is lower with ECMO [61]. However, in the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, the largest trial to date of early use of ECMO in severe ARDS, Coombes et al reported a statistically insignificant 11% absolute reduction in mortality at 60 days [62].

Progression of Supportive Care in Severe COVID

![Figure 1. Cardiovascular complications in COVID.](image1)

Figure 1.

![Figure 2.](image2)

In cardiovascular patients it is important to determine first whether left-sided cardiac dysfunction is present. Timely echocardiographic assessment in the presence of any clinical suspicion of cardiac dysfunction or sign of circulatory compromise should be undertaken [53,58,64]. Pulmonary arterial catheters (PA cath) are helpful for measurements of blood flow, filling pressures as well as for blood gas values from different circulatory compartments.

In high cardiac output states V-A access alone may not be sufficient and eventually a modifications to a hybrid constellation may be indicated (Hybrid ECMO like V-V-A) Shekar K.

Few cases with cardiopulmonary failure were reported using cardiopulmonary support during COVID [65,66]. A myocarditis case in a cardiogenic shock patient that required V-A-ECMO, was reported where an endomyocardial biopsy was undertaken and the virus located in the myocardium for the first time [23].

A recent case reported in a patient with combined cardiogenic and vasoplegic shock using V-A-ECMO and intravascular microaxial blood pump (CP Impella, Abiomed) with the rational to decrease afterload and to increase organ perfusion by increasing pump power and left ventricular unloading with the Impella and V-A-ECMO devices also by reducing the V-A-ECMO related increase in afterload [66]. Regardless of whether the systemic arterial hypotension is thought to be cardiogenic with LV failure, distributive, or mixed shock, the LVEF generally is a useful index to determine whether mechanical circulatory support (MCS) is reasonable. If LVEF is high or even normal in the setting of systemic arterial hypotension, the LVEDV and heart rate are normal, then the cardiac output is normal or elevated, and MCS would have to be able (with native output) to exceed that in order to have a hemodynamic benefit. In contrast, if the LVEF is low, then for a normal LVEDV and heart rate, the cardiac output is reduced despite optimal LV preload, and MCS may be reasonable. If the LVEF is reduced, and high doses of inotropes are required to treat systemic arterial hypotension, the LVEDV and heart rate are normal, then the cardiac output is normal or elevated, and MCS would have to be able (with native output) to exceed that in order to have a hemodynamic benefit. In contrast, if the LVEF is low, then for a normal LVEDV and heart rate, the cardiac output is reduced despite optimal LV preload, and MCS may be reasonable. If the LVEF is reduced, and high doses of inotropes are required to treat systemic arterial hypotension, MCS for the LV may be appropriate in highly selected patients with COVID19.

If a PA cath can be placed expeditiously in patients with shock, they are recommended for the purposes of definitive diagnostics; from PA catheters, the cardiac output and index, LV power/cardiac power output, as well as the PA pulsatility index.
Hybrid V-V/V-A ECMO approaches may be reasonable to ensure oxygenation in the upper body. However, hybrid configurations are more complex and resource-intensive, typically requiring continuous bedside attendance.

**Short-term left ventricular assist devices with either central or peripheral cannulation; short-term catheter-mounted left ventricular assist devices (Impella®, Abiomed)**

The principal advantages of left ventricular assist devices over V-A-ECMO in shock are direct LV unloading, and more homogeneous distribution of blood flow through the systemic arterial circulation. Direct (inflow cannula within the left side of the heart, and particularly the LV) LV unloading is more effective in reduction of LVEDV, and consequently, LV diastolic and systolic pressures; this may be advantageous relative to indirect (inflow cannula proximal to/upstream of the left side of the heart) unloading (eg, via V-A-ECMO) vis-a-vis greater reduction of pathological load-induced signals and resultant mechanotransduction\(^\text{67}\). The effectiveness of V-A-ECMO in unloading the left side of the heart is an area of some controversy with consistently result in augmentation of the LVEDV and LVEDP. What is less controversial regarding LV distension in V-A-ECMO, is that MCS approaches which employ leftsided circuit inflow (direct unloading) generally are more effective in achieving LV unloading than those which employ rightsided circuit inflow.\(^\text{67}\)

Consequently, in some patients, left ventricular assist device-based approaches may be superior to V-A-ECMO. Percutaneous transfemoral placement may be performed at the bedside under echocardiographic guidance, rather than in a cardiac catheterization laboratory. In pandemic conditions, this may be useful. Second, placement via an axillary artery approach, using the newest iteration of introducer sheaths and securing devices may facilitate safer prone positioning. The original Impella 2.5 device generally may not provide adequate flow for the severely compromised shock patient for which robust LV MCS is required. The Impella CP device is better with a peak flow of 4.3 L/m. The Impella 5.0 and 5.5 devices, each of which may be introduced via side-grafts on the axillary artery, are capable of providing flows of 5.0 and 5.5 L/m, respectively, that is, levels of flow close to those achievable with surgically implanted left ventricular assist devices. Experience with Impella in combination with ECMO, that is, “ECPELLA”, to enhance unloading and boost support is just beginning to emerge in severely compromised patients with COVID-19.\(^\text{59}\)

**RV support respiratory failure commonly causes an increase in the pulmonary vascular impedance, increasing RV afterload**

In some cases, this can occur to such an extent (afterload mismatch) that even in the setting of normal intrinsic RV contractility, the RVEF and output may decrease substantially (cor pulmonale). In such patients in the acute setting, attempting to treat the underlying etiology of impaired gas exchange using V-V-ECMO alone, may not be sufficient. This is because V-V ECMO recirculation is exacerbated by reduced RVEF and tricuspid regurgitation. In cases of cor pulmonale with COVID-19-related respiratory failure, we suggest that strategies to support the RV are appropriate. For patients who may require proning, percutaneous RVADs using femoro-femoral approaches, can be used with an oxygenator. The single cannula device (eg, Protek Duo, Livanova) approach to this offers the advantages of peripheral cannulation via one site, and with minimal recirculation. Central approaches may be reasonable in patients in whom high flow rates cannot be achieved. If high flow rates are thought not to be achievable with a single cannula approach, then V-V-ECMO plus a device such as the Impella RP may be reasonable.

Because outcomes are clearly poorer when more organ systems are dysfunctional, we suggest that MCS ought to be highly selectively implemented in patients infected with COVID-19. ECMO is warranted when metrics indicate a high (80%) risk of mortality with conventional management. These notably include Pa O\(_2\)/Fi O\(_2\) ratio below 100, despite available optimal care and need to be avoided in inexperienced centers. Is not a therapy to be rushed to the front lines when all resources are stretched during a pandemic.\(^\text{55,58}\)

Patients without comorbid conditions under age 50 are the highest priority although resources are limited. Standard contraindications apply terminal disease or otherwise highly limited life expectancy at baseline, active biochemical or clini-
cal coagulopathy (particularly that which is unable to be treated or has failed treatment), major CNS damage, do not resuscitate (DNR status), and the absence of consent. Exclusions for COVID-19 during limited resources are hospital-specific. Because prognosis is worse, patients with major comorbid conditions (of note is immunosuppression—either due to disease or iatrogenically), age >70, and mechanical ventilation >7 days, could be reasonably excluded. Anecdotally, renal failure is not an exclusion; however, general outcomes with patients with COVID-19 with renal failure is exceedingly poor in the published Chinese experience69.

CONCLUSION

Compared to other hospitalized patients with COVID-19, those needing intensive care, are more likely to have preexisting cardiovascular diseases or risk factors. Cytokine storm with hyperinflammation correlates with the severity of the disease. It is associated with mortality and is a key factor in determining the clinical course of extrapulmonary multiple-organ failure particularly the cardiovascular system. Advanced Cardiac and Pulmonary Support has been reported in selected a COVID population.

REFERENCES