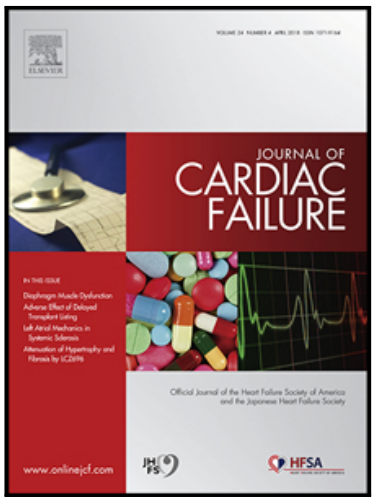

Coronavirus Disease-2019 and Heart Failure: A Scientific Statement From the Heart Failure Society of America

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Coronavirus Disease-2019 and Heart Failure: A Scientific Statement From the Heart Failure Society of America

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Introduction

The first infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) was reported in December 2019. The ensuing and still ongoing pandemic continues to present significant public health challenges with important cardiovascular consequences. Despite the rapid development of effective vaccine programs, coronavirus disease (COVID-19) cases persist with newly evolving longer-term effects. Patients living with heart failure (HF) serve as a particularly vulnerable population wherein worse clinical outcomes ensue in the setting of acute COVID-19. Questions pertaining to mechanisms of disease activity, the unique vulnerability attributable to pre-existing cardiovascular disease, and the natural history of post-acute sequela are the subject of avid ongoing research. Changes in patterns of care for patients with chronic diseases have prompted dramatic shifts in care delivery, with increased reliance on remote monitoring systems and virtual visits. Heart failure care has been uniquely impacted in this regard.

The present document, compiled by a multidisciplinary group of investigators, serves to outline the natural history of COVID-19 and its effects on the heart, pertinent discoveries, implications for clinical care, and remaining gaps in knowledge at the nexus of HF and COVID-19 in adults. As an important disclaimer, new information on COVID-19 steadily emerges. The references and concepts in this paper reflect the state of knowledge at the time of review and writing but are subject to change, predicated on anticipated future discovery. This scientific statement is intended, therefore, to serve as a document whereby progress may be subsequently assessed.

Pathophysiology

Viral Infection and Cardiovascular Disease

Early during the pandemic, it became apparent that infection with SARS-CoV2 resulted in systemic manifestations beyond respiratory compromise, with significant yet heterogenous presentations observed involving the cardiovascular system.[1,2] These ranged from asymptomatic biomarker elevations to HF and cardiogenic shock requiring hemodynamic support.[3–6] Case reports of COVID-19 myocarditis garnered significant attention, yet confirmation of causation has proven elusive.

Myocardial injury and Myocarditis - Defining the Problem

Before delineating mechanisms by which viral infections may lead to cardiac pathologies, it is first critical to review commonly employed terms of myocardial injury or cardiac injury. Myocardial injury can be defined most universally by elevations in serum troponin concentrations,[7] but has also been reported in the context of findings on advanced imaging. Main findings include abnormalities on cardiac magnetic resonance imaging (cMR) in T1 and T2

mapping, and late gadolinium enhancement, among others.[8] The diagnosis of myocarditis, however, rests upon recognition of a clinical syndrome with abnormalities noted across multiple parameters.[9,10] Though pathological assessment of cardiac tissue by endomyocardial biopsy has been emphasized, the sensitivity of findings may vary. Further, it is increasingly recognized that cardiac injury from SARS-CoV-2 may not require myocyte death or an inflammatory cell infiltration.[11,12] Thus, the term myocarditis has been reported in many settings based on varying criteria, including elevation in troponin concentrations, clinical signs of congestion, decrements in ejection fraction, and/or abnormal cMR findings, amongst others, in the absence of other explanatory causes.

Viral Infection and Myocardial Injury

To elucidate the role of viral infection in causing myocardial injury and potentially myocarditis, proposed mechanisms range from direct cellular invasion to active induction of detrimental immune responses (inflammatory or autoimmune). Endemic viruses such as coxsackie A and B, echoviruses, parvovirus B19, and viruses from the Herpesviridae family (such as human herpesvirus 6 (HHV6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)) display primary cardiovascular tropism or lymphotropism and persistence in cardiac tissue, whereas human immunodeficiency virus (HIV), influenza A and B virus infections can also result in myocardial injury and myocarditis by enhanced immune system activation.[12–15] Epidemic H1N1 influenza strains such as the causative agent in the 1918 pandemic or the 2019 H1N1pdm09 virus have been correlated with myocarditis, with histological studies in the latter displaying degenerated myocytes, infiltration of lymphocytes, and interstitial edema, but less often viral infiltration in myocytes itself.[16] Seasonal coronaviruses have not previously been associated with cardiac abnormalities. In contrast, myocarditis and cardiomyopathy have now been reported with all three epidemic-prone beta-coronaviruses: Middle East Respiratory Syndrome (MERS) virus and Severe Acute Respiratory Syndrome associated coronaviruses (SARS-CoV and SARS-CoV-2).[17–20] Infiltration of macrophages has been reported,[21] but autopsy studies and some endomyocardial biopsy reports in cases of severe or fatal SARS-CoV-2 infections have not commonly demonstrated classic lymphocytic myocarditis based on Dallas or European Society of Cardiology (ESC) working group criteria.[9,10,22,23]

Compared to SARS-CoV, SARS-CoV-2 targets angiotensin-converting enzyme 2 (ACE-2) receptors with greater affinity and across a broader range of organ systems, allowing its spike protein to gain cell entry mediated by host serine proteases TMPRSS2, cathepsin B, and cathepsin L.[24–26] ACE-2 is expressed on a large variety of cardiac cells including cardiomyocytes, pericytes, fibroblasts, and endothelial cells, as well as infected leukocytes and macrophages discovered in the myocardium.[27] The latter suggests localization of virus to the heart at least during transient viremia.[28] The proposed mechanisms of cardiac injury in COVID-19 patients include direct infection with fusion of myocytes and apoptosis of cardiac and vascular endothelial cells, damage via pro-inflammatory dysregulated cytokine storm in response to the infection, and propensity towards the development of micro-embolic and thrombotic involvement in

vasculature.[12,20,29,30] Rare cases of acute myocardial infarction with high thrombus burden were reported in patients with COVID-19 and may have also contributed to ventricular dysfunction and, in some cases, cardiogenic shock.[31–33] Additionally, due to reports of SARS-CoV-2 preceding autoimmune and autoinflammatory conditions such as multisystem inflammatory syndrome in children (MIS-C) and adults (MIS-A), the role of infection leading to an immune response against self-epitopes has also been invoked.[34–37] Secondarily, respiratory dysfunction and hypoxemia, as well as dysregulation of the renin-angiotensin-aldosterone system (RAAS), likely also contribute to cardiac findings in patients with COVID-19.[12] Thromboembolic complications such as deep vein thrombosis and pulmonary emboli, in addition to rises in pulmonary pressures from COVID-19-induced parenchymal lung disease leading to right heart failure have also been described.[38,39]

While precise pathophysiologic pathways may be multifactorial and incompletely understood, myocardial injury is more commonly encountered amongst patients with pre-existing cardiovascular (CV) disease and is associated with worse clinical outcomes, including admission to the intensive care unit (ICU), ventricular dysfunction, arrhythmias, and death in patients with COVID-19. The degree of myocardial injury and myocardial stretch, as evidenced by cardiac troponin and natriuretic peptide elevations, have further shown to be strong predictors of adverse outcomes.[4,40–42]

COVID-19 in Patients with a History of HF

Early in the pandemic, advanced age and cardiometabolic comorbidities including diabetes, obesity, and hypertension were observed to be commonly associated with more severe forms of COVID-19.[43,44] Mechanistic understanding of SARS-CoV2 viral entry via the ACE-2 receptor led to concerns that patients with preexisting dysregulation of this neurohormonal axis, including patients with HF, may be particularly susceptible to severe COVID-19 and its related complications.[45–47] This concern for increased susceptibility was reinforced by historical presentations of cardiac findings in other viral respiratory infections, such as influenza. For example, in a retrospective analysis of over 8 million individuals with HF from the National Inpatient Sample, those diagnosed with influenza during hospitalization had higher rates of in-hospital mortality, acute respiratory failure, and acute renal failure even after propensity matching.[48] Together, these data identified patients with HF as possibly more vulnerable to serious adverse events associated with COVID-19.

The incremental risk of poor in-hospital outcomes in patients with COVID and HF history has been demonstrated in two large retrospective studies. One analysis of 6,439 patients admitted with COVID-19 across a large health system in New York City from February to June 2020 included 422 (6.6%) patients with HF. The study found that a history of HF was associated with prolonged length of stay, increased need for ICU level of care, and greater rates of mechanical

ventilation. Overall mortality among the cohort was 25.8%, though those with pre-existing HF had significantly higher mortality as compared to those without (40.0% vs. 24.9%; hazard ratio [HR] 1.88, 95% confidence interval [CI]:1.27 to 2.78).[49] Importantly, the effect of prior history of HF on worsening outcomes was observed across the spectrum of left ventricular ejection fraction and RAAS inhibitor use. Similar findings were reported using in a large, all-payer database inclusive of >1,000 health care entities and health systems which included 132,312 patients with HF hospitalized from April to June 2020.[50] Those with a history of HF and hospitalization with COVID-19 had significantly greater in-hospital resource utilization, including higher rates of ICU admission, mechanical ventilation and renal replacement therapy as compared to those hospitalized with COVID-19 without HF. Among patients hospitalized with COVID-19, 24.2% of those with a history of HF died compared to 14.2% without a history of HF. In addition to increased mortality, history of HF also predicted greater morbidity in those hospitalized with COVID-19, with 41.0% of survivors requiring post-acute care services as compared to 18.6% among those hospitalized with COVID-19 without a history of HF.[50] Overall, these data suggest that patients with a history of HF (regardless of ejection fraction) represent a vulnerable group with greater predilection for COVID-19-related morbidity and mortality (Central Figure).

Recognition of Acute Heart Failure in Patients with COVID-19

Challenges in recognition of HF may be encountered due to overlapping symptoms with respiratory compromise typically associated with COVID-19, including shortness of breath and pulmonary infiltrates on imaging. For example, both HF and pneumonia in the setting of COVID-19 can present with ground-glass opacities and thickened interlobular septae. Assessment of congestion, including signs and symptoms, as well as objective evidence either by elevated natriuretic peptides or pulmonary congestion on imaging, should occur routinely to help distinguish possible presenting features of HF; however natriuretic peptides may also be elevated in the setting of pulmonary embolism or acute respiratory distress syndrome.[51] In cases of suspected HF, pleural effusions, cardiomegaly, pulmonary vein enlargement maybe be more apparent and readily resolved with diuretic therapy.

Despite the aforementioned diagnostic limitations, assessment of congestion is relevant not only for those patients with a history of HF but also in identifying new or incident HF. The point prevalence of new HF diagnoses in the setting of COVID-19 has not been well reported; however, observational studies suggest SARS-CoV2-related incident HF is likely infrequent. In an adjunct study of the same 6439 patients hospitalized with COVID-19 in New York City, only 37 (0.6%) were discharged with a new diagnosis of HF.[49,52] Of these, 13 presented with shock (cardiogenic (n=4), septic (n=6), mixed (n=3)) and 5 patients presented with acute coronary syndrome. Notably, only eight patients had neither CV disease nor any CV risk factors, whereas

14 had a history of overt CV disease, and the other 15 had one or more risk factors that could have predisposed to the development of HF. The eight individuals with new HF in the absence of CV risk factors tended to be younger, with lower body mass indices and fewer comorbidities than other new HF diagnosis patients.

Evidence of Myocardial Injury in the Subacute Setting

Mechanisms of viral injury leading to myocardial edema or fibrosis have been described to explain the high rates of left ventricular diastolic and systolic dysfunction in patients without epicardial or microvascular occlusions.[53] In the subacute setting, cMR has revealed a high frequency of cardiac involvement in various forms, including changes in systolic function, raised myocardial native T1 representing potential capillary leak, fibrosis in addition to raised myocardial native T2 typically indicative of myocardial edema, myocardial late gadolinium enhancement indicating fibrosis, or pericardial enhancement.[19] For example, in a recent case series of 148 patients with positive troponin and severe COVID-19 in hospitals in London, 54% of hospitalized patients had MRI abnormalities at a mean of 68 days after discharge, with 32% inflammatory and 28% ischemic patterns.[8] A majority of patients (89%) had normal LV function (ejection fraction 67% +/- 11). The rate of cMR abnormalities in young, previously healthy athletes who survived COVID-19 infection appears much lower, between 0.6 and 3%.[54] Increased recognition of cardiac involvement as evidenced by advanced imaging techniques point to direct and indirect effects of SARS-CoV2 infection on the cardiovascular system that may reflect new HF or potential for the development of HF over time.[55]

Management of Heart Failure During the COVID-19 Pandemic

Medical Management

Despite aforementioned concerns regarding a potentially increased propensity for more severe disease by way of enhanced viral entry via upregulated ACE2 receptors in patients on RAAS pathway inhibitors,[47] accumulating retrospective and prospective data as well as a joint statement by the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA) affirm that RAAS pathway inhibitors should generally not be discontinued in patients with HF who are at risk for or hospitalized with COVID-19.[56–59] In fact, discontinuation of these medications in patients not only with HF but also hypertension and coronary artery disease has not been shown to improve outcomes and likely deprives patients of evidence-based therapy.[57]

Statins have been studied as treatment in COVID-19. Multiple observational studies have shown improved outcomes among patients on chronic statin therapy who are hospitalized for COVID-19, potentially due to their pleiotropic and anti-inflammatory effects,[60–62] while randomized clinical trials are ongoing or will soon be reported. Patients with an alternative indication for statin therapy should remain on therapy, as there is no evidence that halting of statins is beneficial in patients with COVID-19. In light of the known pro-thrombotic state associated with COVID-19 infection, various anticoagulation strategies are under investigation. Although retrospective data suggested benefits for intermediate- or full-dose anticoagulation,[63] prospective studies have shown different findings based on disease severity.[64–66] At a minimum,

all hospitalized HF patients with COVID-19 infection should receive prophylactic doses of anticoagulation, and some may benefit from therapeutic anticoagulation.[67] Those with an alternative indication for therapeutic anticoagulation should continue this therapy provided there are no contraindications. Randomized control trial data have also informed the utility of corticosteroids in improving 28-day mortality amongst patients hospitalized with COVID-19.[68] In an open-label trial of dexamethasone (intravenous or oral), 28% of patients had some form of heart disease. Patients with HF should be offered steroids among those requiring oxygen or invasive mechanical ventilation. Similarly, antiviral agents, monoclonal antibodies, and/or other immunomodulating therapies (i.e., tocilizumab) should be offered to patients with HF in the appropriate clinical settings. Special attention may need to be paid to effective circulating volume in the setting of such therapies, particularly in patients with HF on chronic diuretic therapy.

Therapy	Key pharmacologic considerations among Patients with Heart Failure & COVID-19
RAAS inhibition (ACEi, ARB, ARNI)	*RAAS inhibition and guideline-directed medical therapy **should not** be disrupted in the acute setting of COVID-19 or thereafter*
Statin	*Currently, insufficient evidence to support routine statin use without other indications for statin therapy. However, patients on statin therapy should not have care disrupted*
Anticoagulation	*Evidence to guide recommendations as to optimal anticoagulation regimens for patients with HF has been recently completed with further data are forthcoming; recommendations may be different based on the severity of disease (moderate vs. critically ill) per ACTIV-4 findings*
Steroids & Immunomodulating therapies (Intravenous immunoglobulin) or monoclonal antibodies	*May require careful monitoring of volume status and additional decongestive therapy as indicated*
Antiviral agents	*No evidence to support differential approach to use among patients with HF*

Temporary Mechanical Circulatory Support

Data regarding the use of temporary MCS for patients with COVID-19 and cardiogenic shock are primarily limited to case reports and small case series.[69–71] Cardiogenic shock in patients with COVID-19 should thus be managed similarly to those without COVID-19, with appropriate pharmacological therapies selected based on clinical presentation. If MCS is indicated, veno-arterial extracorporeal membrane oxygenation (VA ECMO) is often preferred for hemodynamic support as well as oxygenation, as most patients have significant coexisting pneumonia. In

ARDS with profound hypoxemia, differential oxygenation gradients may exist between blood traveling through the native circulation (arising from cardiac ejection) and the ECMO pump. In such scenarios, conversion to veno-arterial-venous (VAV) ECMO cannulation strategy can be considered to deliver fully oxygenated blood through the pulmonary circulation while preventing compromise to cardiac recovery. Although data remains limited, the Extracorporeal Life Support Organization (ELSO) put forth specific guidelines regarding ECMO use in patients with COVID-19.[72] In one report of 22 patients with COVID-19 on ECMO, 21 patients had respiratory failure while 7 had cardiac failure requiring arterial support.[73] Ultimately, 12 patients (54.5%) survived hospitalization. ELSO suggests that pre-pandemic criteria for selection for ECMO candidates should be used; however, these may not be universally applicable if resources are constrained.[72]

Impact of Pandemic on Evaluation for Advanced Heart Failure Therapies

The pandemic has also impacted care for patients with HF without COVID-19 due to significant changes in healthcare delivery.[67] The early phases necessitated a reallocation of various hospital resources, increasing use of telemedicine, and placing limitations on elective procedures and testing. Thus, less urgent evaluations for left ventricular assist devices (LVAD) and heart transplantation (HT) faced significant delays.[74] For example, cardiopulmonary exercise testing was often deferred since this test is an aerosolizing procedure and therefore requires special precautions. Similarly, placement of implantable cardioverter-defibrillators (ICDs), stress testing, right heart catheterization, and other non-emergent diagnostic and therapeutic procedures were postponed early on and subsequently depending on COVID-19 case volume.[74] Care adaptations have since largely allowed for resumption of these services in many hospitals but still require negative pre-procedural COVID testing.

Left Ventricular Assist Devices

As the pandemic continues with varying densities of infection, decisions regarding new implantation of durable LVADs were and continue to be highly dependent on various factors, including local policies, rate of SARS-CoV-2 infection in the surrounding area, and the availability of relevant resources, including ICU capacity. In settings of high rates of SARS-CoV-2 infection placing strain on hospital resources, LVAD implantation should be limited to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) status 1-3 patients in whom implantation has unequivocal benefit among appropriately selected patients.[75] Considerations should be given to the feasibility of outpatient LVAD follow-up care in the early post-operative period to minimize the risk of exposure to SARS-CoV-2. The social evaluation is particularly relevant and should include an assessment of home conditions that may place patients at increased risk for acquiring COVID-19 in the vulnerable post-operative phase.

Special considerations are required for patients on LVAD support who contract COVID-19.[76]This population is at risk for severe COVID-19 infection due to advanced age (in many circumstances), increased number of comorbid conditions, and potentially compromised

cellular immunity leading to a functionally immunosuppressed status.[77] Cases have been reported of COVID-19 complicated by cytokine release syndrome leading to ARDS and multiorgan failure.[78] Additionally, COVID-19 infection is associated with a pro-inflammatory and pro-thrombotic milieu which could pose additional problems in LVAD supported patients who are already at increased risk for stroke and thrombosis. In cases of COVID-19 pneumonia-associated RV dysfunction, adjustments may need to be made to LVAD speed considering inotropic support for the right ventricle. Prone positioning may present unique challenges in patients with LVADs due to fear of driveline displacement or worsening of right ventricular hemodynamics,[79] but is reported to have been conducted safely in highly monitored settings.[75]

Cardiac Transplantation

Heart transplant waitlist activity and volume were also impacted during the peak of the COVID-19 pandemic in the United States. Particularly during the early months, there was a significant increase in inactivated transplant candidates, with fewer new candidates added to the waitlist.[80] Donor recovery also decreased due to concerns regarding potential for COVID-19 positivity, initial lack of access to COVID-19 testing, and limitations in organ procurement organizations (OPO) operation in the setting of COVID-19 associated policies around limited hospital access and travel. The number of heart transplants performed concomitantly declined even in regions with a lower prevalence of COVID-19 due to the effects of organ sharing.[80] At many centers, only patients requiring hospital admission who qualified as UNOS tiers 1-3 remained active on the transplant list wherein the risk of mortality due to HF was deemed to outweigh the risk of COVID-19 exposure and need for resource conservation.[81]

The pandemic catalyzed many centers to switch to noninvasive surveillance strategies for ambulatory transplant recipients to detect rejection. Use of gene expression profiling and measurements of donor-derived cell-free DNA minimized exposure to healthcare personnel,[82,83] mainly as endomyocardial biopsies were performed more selectively. Downstream clinical implications of this modified workflow on rejection rates and graft function and associated survival outcomes in heart transplant recipients are of importance and undergoing further study.

The impact of COVID-19 infection among heart transplant recipients have been published in select reports. Amongst these, two New York Hospitals reported outcomes of 28 and 22 patients, respectively, and a group from Italy reported on 47 heart transplant recipients diagnosed with COVID-19. All three groups reported a case fatality of 25 to 30%, highlighting the need for extra caution as to the avoidance of exposure to COVID-19 in heart transplant recipients, as well as the need to triage to higher levels of care if COVID-19 is contracted for such immunocompromised patients.[84–86] A recent study of 99 patients with heart transplants and COVID-19 found a death rate of 15% and 64% required hospital admission[87]. Concerning immunosuppression, reducing the dosage of calcineurin inhibitors and reducing or temporarily discontinuing antimetabolites in the setting of COVID-19 infection may be considered on an individual basis. Yet, data as to optimal approaches are lacking.[88] Additionally, drug interactions with COVID-19 therapeutics should be reviewed. Current vaccines against SARS-CoV-2 appear less effective in immunosuppressed patients,[89,90] stressing the importance of continued

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