VIEWPOINT

COVID-19 and Heart Failure With Preserved Ejection Fraction

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Editorial page 1506

Related articles pages 1512 and 1522

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Patients with preexisting cardiovascular disease (CVD) who develop coronavirus disease 2019 (COVID-19) have worse outcomes than patients without CVD.[1] Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can directly or indirectly lead to myocardial injury. Although fulminant viral myocarditis due to COVID-19 appears to be uncommon, recent data, although limited, suggest that direct myocardial injury may occur in some individuals.

This Viewpoint contextualizes the emerging data on the risk of heart failure, particularly heart failure with preserved ejection fraction (HFpEF), in patients during both the acute phase of COVID-19 illness and the chronic phase of recovery in COVID-19 survivors. This is important to elucidate, because infection with COVID-19 may be associated with HFpEF through several pathways: COVID-19 may cause HFpEF via direct viral infiltration, inflammation, or cardiac fibrosis; it may unmask subclinical HFpEF in individuals with underlying risk factors; or it may exacerbate preexisting HFpEF. Key issues are discussed involving the link between COVID-19 and risk of HFpEF due to their shared inflammatory pathophysiology and cardiometabolic risk profiles (**Figure**) and the potential for an increase in the individual- and population-level effects of HFpEF in the aftermath of the pandemic.

Myocardial Complications in Acute COVID-19

Evidence of direct myocardial injury in COVID-19 is supported by elevated biomarker levels, cardiac imaging, and autopsy series. In early studies of the COVID-19 pandemic, approximately 20% to 35% of hospitalized COVID-19 patients were noted to have elevated cardiac biomarker levels (troponin, natriuretic peptides), and these elevations have been associated with higher mortality.[2] Echocardiographic assessment during hospitalization for COVID-19 has demonstrated primarily preserved ejection fraction with 2 key findings: right ventricular abnormalities and left ventricular diastolic dysfunction. In an echocardiographic study of 100 patients with COVID-19 in Israel (mean age, 66 years), left ventricular ejection fraction was normal in 90%, and the most common abnormalities were right ventricular dilation (39%) and left ventricular diastolic dysfunction (16%).[3] Similar findings were observed in a study of 105 hospitalized COVID-19 patients from New York City with similar age distribution (mean age, 66 years).[4]

The mechanism of right ventricular dilation and dysfunction is likely multifactorial and includes sequelae of hypoxemic respiratory failure and thrombotic events. The left ventricular diastolic dysfunction may be related to preexisting subclinical HFpEF given the older age of these patients, or it may reflect a novel acute process that has either resulted from the inflammatory milieu, intravascular coagulation, or hypoxemia leading to microvascular ischemia. Whether the latter is the predominant proportion of cases is unknown. A study from Germany reported high rates of abnormal findings on cardiac magnetic resonance imaging in 78 of 100 patients after recovery from COVID-19 illness; however, the generalizability of these data are unclear.[5] Another report from Germany based on autopsy findings that analyzed cardiac tissue from 39 patients who died of COVID-19 found that SARS-CoV-2 was detectable in 62% of specimens, suggesting high incidence of viral presence in the myocardium.[6] However, a key question remains whether the myocardial injury and inflammation that have been observed are related to the direct viral injury or systemic immune reaction secondary to infection.

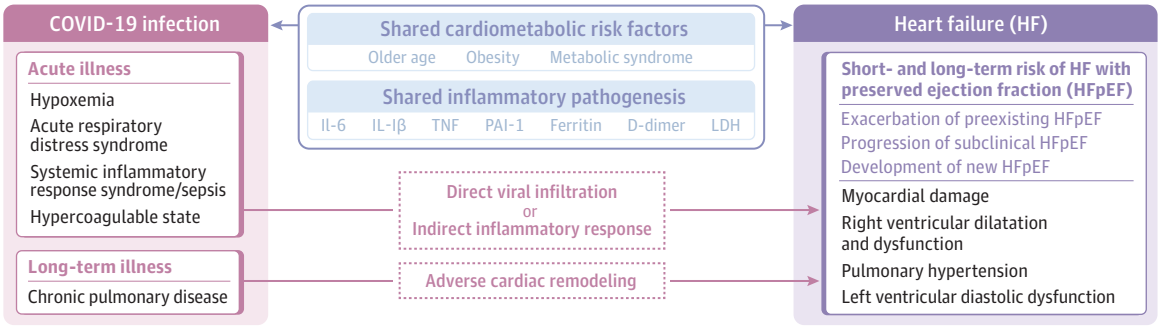
Inflammation as a Central Contributor to COVID-19 and HFpEF

The central pathogenesis shared by both COVID-19 and HFpEF appears to be inflammation. Infection with SARS-CoV-2 causes the release of proinflammatory cytokines such as IL-1 and IL-6 that affect the respiratory system but also directly and indirectly affect the myocardium. Existing data have established the role of inflammatory cells and pathways during an acute primary injury to the myocardium, such as an ischemic insult or a viral injury (eg, influenza) contributing to HFpEF. In observational cohort studies conducted prior to the COVID-19 pandemic, plasminogen activator inhibitor (PAI-1), which is also an integral regulator of the fibrinolytic system, has been reported to be released in response to other respiratory viruses and has also been found to be associated with higher risk of HFpEF in the general population in the absence of infectious triggers.[7]

Overlapping Cardiometabolic Profiles of Risk

In addition to shared pathophysiology, COVID-19 and HFpEF have shared cardiometabolic risk profiles. Obesity has been highlighted as an important risk factor for COVID-19 severity.[8] This risk is particularly relevant given the high age-adjusted prevalence of obesity of Western countries, estimated at 42.4% in the US, 28% in the UK, and 20% in Italy, compared with lower rates in Eastern nations, estimated at 6% in China and 4% in Japan.[9] Prior to COVID-19, prevalence and incidence of HFpEF were increasing, with HFpEF accounting for more than 50% of prevalent heart failure cases. The mean annual percentage increase of HFpEF between 2005-2014 ranged from 7% to 10% per year for Black men and women, respectively, compared with 5% per year for White adults, based on the Atherosclerosis Risk in Communities study.[10] These increases are driven, in part, by the aging population and increases in prevalence of obesity and diabetes. This same group of older individuals with cardiometabolic risk factors who are at-risk for HFpEF are also those who are

Figure. The Potential Intersection of Acute and Chronic Phases of COVID-19 and Risk of Heart Failure With Preserved Ejection Fraction



COVID-19 indicates coronavirus disease 2019; LDH, lactate dehydrogenase; PAI-1, plasminogen activator inhibitor 1; TNF, tumor necrosis factor.

experiencing greater rates of severe COVID-19 infections. It is possible that the acute viral stressor of COVID-19 also may trigger the vulnerable myocardium in this susceptible subset of the population with cardiometabolic risk factors and increase the likelihood of HFpEF during the acute illness or following recovery.

Unmasking and Potentiation of Long-term HFpEF Risk

Beyond acute COVID-19 illness, there may be long-term cardiac effects of COVID-19 infection. First, it is possible that acute illness with COVID-19 may be a precipitating factor that could contribute to progression of preexisting, but previously asymptomatic, subclinical HFpEF to symptomatic, overt clinical disease. Second, there is the unanswered question regarding the potential of persistent myocardial damage caused by COVID-19 that may be associated with future risk of developing HFpEF, for which long-term data are needed. Multiethnic population-based cohort studies with detailed cardiovascular phenotyping data collected before the pandemic are well-poised to distinguish the former from the latter in COVID-19 survivors with longitudinal studies. COVID-19 survivorship may represent a novel, independent risk factor for the development of HFpEF, much like the recognition that HIV-associated cardiomyopathy may manifest primarily as subclinical diastolic dysfunction. Many survivors of COVID-19, particularly those who have recovered from severe illness with profound hypoxemic respiratory failure and thromboembolic complications, will be at risk for chronic right heart failure, pulmonary hypertension, and diastolic dysfunction. These adverse cardiac structural and functional changes may occur both due to myocardial impairment during the acute infection and as a result of chronic pulmonary disease.

Conclusions

There may be a relationship between COVID-19 and HFpEF. SARS-CoV-2 may cause HFpEF, may unmask subclinical HFpEF, or may exacerbate existing HFpEF. Although case reports have described profound COVID-19 myocarditis leading to HFpEF, the more common manifestation in the COVID-19 era may be HFpEF related primarily to the unmasking of subclinical HFpEF and secondarily to the development of new HFpEF following infection with SARS-CoV-2. COVID-19 should be recognized as a potential risk factor for HFpEF, prompting screening and treatment to prevent further progression and adverse outcomes on an individual level and to mitigate the increasing morbidity, mortality, and disparities related to HFpEF.

ARTICLE INFORMATION

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