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Perspective

COVID-19 and the Heart: Lessons Learned and Future Research Directions

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Abstract: It has become evident that acute COVID-19 infection can lead to cardiovascular complications. While the exact mechanisms by which COVID-19 affects the cardiovascular system have yet to be fully elucidated, several mechanisms have been proposed, including direct myocardial effects on the virus and systemic inflammation as an indirect result. The cardiovascular complications of COVID-19 have been characterized and described using noninvasive cardiac imaging. The impact of COVID-19 on the cardiovascular system extends beyond the acute phase of the infection and well beyond recovery or the convalescent period. However, the underlying mechanisms of post-viral long-COVID symptoms have yet to be elucidated. It is evident that COVID-19 has become endemic and is here to stay. Future studies are needed (1) to understand the long-term effects of the cardiovascular complications of COVID-19, future cardiovascular events and the impact of mutating variants on cardiovascular complications through data collection and analysis, (2) to identify the most important diagnostic criteria for prognosis of COVID-19 and to understand the disease mechanism through biomarkers and advanced cardiac imaging, including echocardiography and (3) to develop novel strategies to manage and treat these cardiovascular complications using the knowledge gained.

Keywords: COVID-19; cardiovascular disease; long–COVID syndrome; cardiac imaging

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic—caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has brought new focus and attention to the impact of the disease on pulmonary and other organ systems, including the cardiovascular system. It has become evident that acute COVID-19 infection can lead to cardiovascular complications [1–5]. Individuals with pre-existing cardiovascular conditions are more likely to experience complications from COVID-19. They also have an increased risk of developing new cardiovascular diseases [1–5]. In addition, clinical outcomes are worse in patients with COVID-19 with cardiovascular disease [6]. Furthermore, acute cardiac injury is commonly reported among patients hospitalized with COVID-19 and is associated with severe clinical outcome, including need for mechanical ventilation and death [1,7]. However, while we know more about COVID-19 and its effects on the heart than we did at the beginning of the pandemic, many things remain uncertain [8]. In this perspective, we will discuss the relations between COVID-19 and heart disease from clinicians' point of view, including the epidemiology, proposed mechanisms, cardiac manifestations, vaccinations and their impact on outcomes, and the long-term effects of COVID-19 on cardiovascular health.

2. COVID-19 and the Heart: Lessons Learned

Individuals with cardiovascular disease or risk factors for cardiovascular disease, such as obesity, smoking and hypertension, have higher rates of COVID-19 hospitalization [1,4]. Of those who have been hospitalized, severe COVID-19 has been shown to be more likely in the people with underlying cardiovascular diseases [9–11]. A study in China showed

that the risk of severe presentation of COVID-19 is higher in older adults with medical history of cardiovascular disease [6]. Furthermore, when patients were admitted to the hospital, a high number of them experienced cardiovascular events. In fact, more than 11% of hospitalized patients experienced an acute cardiac event during a COVID-19-associated hospitalization, according to a nationwide study conducted in the United States [9]. A report from a high-volume health system in New York showed that nearly one-third of patients hospitalized with COVID-19 experienced acute myocardial injury [12].

While the exact mechanisms by which COVID-19 affects the cardiovascular system have yet to be fully elucidated, several mechanisms have been proposed, including direct myocardial effects of the virus and systemic inflammation as an indirect insult [1,3,11–17]. Severe COVID-19 infection is characterized by disruptions in both the immune and coagulation systems [1,13]. These immune responses involve T-cell lymphopenia, which can last for several months following the onset of the disease [14]. Coagulopathy is a significant contributor to the disease severity and death rate in COVID-19 patients [13,15]. The virus can trigger an inflammatory response, increasing NLRP3 inflammasome activity, which can lead to the induction and perpetuation of a "cytokine storm" in the bodies of SARS-CoV-2 patients, leading to cytokine-related injury and systemic inflammation [16]. This systemic inflammation can have negative effects on the cardiovascular system, promoting the development or exacerbation of cardiovascular diseases. It can lead to endothelial dysfunction, vascular inflammation, and plaque instability, increasing the risk of atherosclerosis and thrombosis [17]. Furthermore, the inflammatory response can cause damage to the heart muscle, leading to myocardial injury and fibrosis [7,18]. Systemic inflammation, particularly that of neutrophils, plays a prominent role in thrombosis of the heart in patients with COVID-19 [19–21]. Cyclic thromboembolism manifesting in acute COVID-19 infection has a significant impact on mortality and morbidity [22]. Autopsy study series also have consistently shown that hypercoagulability of the blood caused by neutrophil results in thrombotic events, while endothelium cell activation has not been seen consistently in the literature [19,23,24].

Chronic inflammation damage could be exacerbated by the presence of viral reservoirs in vital organs, including the heart, even after recovery from COVID-19 [22]. The severity of the acute disease could be heightened by activated inflammatory pathways, which can impair endothelial function through increased production of reactive oxygen species and uncoupling of endothelial nitric oxide synthase (eNOS) [25,26]. As a result, inflammation in the heart tissue continues and can lead to myocardial fibrosis [25,26]. The COVID-19 pandemic may have induced a range of cardiac conditions in a larger population, with symptoms ranging from decreased ventricular compliance due to increased stiffness to diminished contractility because of impaired myocardial perfusion, and the creation of an arrhythmogenic substrate due to inflammation, fibrosis and hypoperfusion [27]. It remains unclear what the future holds about inflammation due to acute COVID infection and the risk of future cardiovascular disease.

The cardiovascular complications of COVID-19 have been characterized and described using noninvasive cardiac imaging [28]. One study demonstrated that about half of patients screened with a transthoracic echocardiogram (TTE) exhibited an abnormality, with these findings leading to a management shift in almost one-third of cases [29]. The detection of echocardiographic anomalies, such as left ventricular (LV) or right ventricular (RV) systolic dysfunction, carries significant prognostic implications in COVID-19 patients [30]. In a separate study, roughly 30% of patients, who exhibited abnormalities in an echocardiography and abnormal biomarkers, died during hospitalization [31].

Decreased LV ejection fraction (LVEF) is associated with a higher inpatient mortality rate in COVID-19 patients [32]. Echocardiography has played a key role in assessing the severity and potential causes of LV systolic dysfunction in COVID-19 infection, such as acute coronary syndrome, Takotsubo cardiomyopathy, myocarditis and multisystem inflammatory syndrome. A diagnosis of acute coronary syndrome with LV systolic function should be considered if a patient presents with chest pain, abnormal cardiac biomarkers

and/or ischemic ECG changes along with a regional wall motion abnormality in a coronary distribution. Stress (Takotsubo) cardiomyopathy should be suspected in those with the classic echocardiographic sign of preserved basal wall thickening but hypokinesis, akinesis or dyskinesis of the mid-apical myocardium [33]. Myocarditis and multisystem inflammatory syndrome, which can occur in adults or children, are other significant causes of LV systolic dysfunction in acute COVID-19 patients [34]. These conditions often present as LV systolic dysfunction along with systemic symptoms such as elevated inflammatory markers, fever, and gastrointestinal symptoms [31].

LV diastolic dysfunction has also been reported in patients with acute COVID-19 [32]. However, in these patients, COVID-19 infection may be one of the many factors that causes LV diastolic function, as risk factors for severe COVID-19 such as advanced age, hypertension, diabetes, obesity and coronary artery disease also overlap with those for diastolic dysfunction. Although COVID-19 causes diastolic dysfunction in the absence of systolic dysfunction, the mechanism behind this remains uncertain. It might be associated with generalized myocardial injury, microvascular dysfunction, or small-vessel vasculitis, all of which have been observed in COVID-19 patients [35].

Notably, the incidence of right ventricular (RV) dilation and systolic dysfunction in acute COVID-19 infection is greater than the incidence of left ventricular (LV) systolic dysfunction [29,36,37]. One study from Italy showed that acute respiratory distress syndrome and patients' mortality were significantly associated with RV systolic dysfunction among COVID-19 patients [38]. COVID-19 infection can lead to RV dilation and systolic dysfunction through various potential mechanisms, such as myocardial ischemia, myocarditis and stress cardiomyopathy. Additionally, acute pulmonary hypertension can cause RV systolic dysfunction [39]. Acute respiratory distress syndrome, pneumonia and pulmonary thromboembolism are the most common causes of acute pulmonary hypertension in COVID-19 infection [40,41]. Echocardiography is the preferred method for determining the severity of pulmonary hypertension and providing differential diagnoses regarding the cause of elevated pulmonary pressures [42].

The impact of COVID-19 on the cardiovascular system extends beyond the acute phase of the infection and well beyond recovery or the convalescent period. Globally, many patients who have recovered from COVID-19 have continued to experience symptoms indicative of possible cardiac involvement, such as dyspnea, chest pain and palpitations [43–45]. This has led to the introduction of terms like "long-COVID" (symptoms lasting more than 4 weeks post-infection) and "post-COVID syndrome" (symptoms persisting for more than 12 weeks post-infection) [46]. Long-term complications in patients with COVID-19, particularly those with pre-existing cardiovascular disease, have also been reported [45]. In a cohort study of over 45,000 hospitalized COVID-19 patients in England [47,48], the risk of major adverse cardiovascular events was about three times higher than in a matched cohort, even in cases of mild disease. Another cohort study of over 150,000 patients [43] from VA hospitals in the US showed that individuals with COVID-19 are at a heightened risk of developing various types of cardiovascular disease beyond the first 30 days post-infection. This includes conditions such as cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease. Importantly, these risks and burdens are present even in individuals who did not require hospitalization during the acute phase of their COVID-19 infection [43].

The underlying mechanisms of post-viral long-COVID symptoms have yet to be elucidated. Recently, researchers found that long-COVID symptoms are associated with serotonin reduction [49]. There are three mechanisms through which viral infection and inflammation driven by type I interferon decrease serotonin: by decreasing the intestinal absorption of tryptophan, a precursor of serotonin; by causing hyperactivation of platelets and thrombocytopenia, which affects the storage of serotonin; and by increasing the turnover of serotonin mediated by monoamine oxidase (MAO) [49]. This reduction in peripheral serotonin subsequently hampers the functioning of the vagus nerve, which in turn, disrupts hippocampal responses and memory [50]. To this day, the clinical mechanisms for long

COVID for increased cardiovascular diseases are not entirely clear [51]. A cross-sectional study of echocardiography and right heart catheterization from Italy implied that long-COVID symptoms were associated with RV dysfunction [52]. Early MRI studies [48,53,54] have shown a persistence of minor cardiac injuries post-recovery, though these studies did not present baseline imaging and control comparisons. Several longitudinal analyses have also evaluated the prevalence of post-COVID myocardial injury. In the World Alliance Societies of Echocardiography COVID study, 198 patients with acute COVID-19 had a follow-up transthoracic echocardiogram at a mean of 129 days. Overall, there was no significant change in left ventricular ejection fraction (LVEF) from baseline, though some variability was noted based on initial LV and RV systolic function [55]. Another study [56] using cardiopulmonary exercise testing combined with stress echocardiography found that abnormally low peak oxygen consumption was common three months post-recovery, often due to reduced stroke volume reserve and chronotropic incompetence, rather than LV or RV systolic dysfunction. An additional study in India [57] noted a significant decrease in LV systolic and diastolic function three months post-recovery. In this study, patients who had moderate to severe disease were more likely to experience long-term LV and RV deterioration. As shown, longitudinal echocardiographic studies have yielded inconsistent results. This may be attributed to the relatively shorter follow-up duration and/or to the differences in the patient groups studied (those who were hospitalized versus those who were not, and those with mild versus severe acute symptoms). Future research needs to clarify whether these changes persist or if they can be reversed over a longer period.

COVID-19 vaccination is effective in reducing the risk of severe illness and hospitalization [58]. Since having cardiovascular risk factors is associated with high risk of COVID-19 related death, COVID-19 vaccination has been associated with a decreased risk of severe illness and hospitalization [59]. While vaccines have known side effects [59–61], most research indicates that the advantages of vaccination surpass the potential risks [62,63]. The administration of COVID-19 vaccines has had a profound impact on public health, as evidenced by a significant decrease in hospital encounters for respiratory infections, SARS-CoV-2 infections, and COVID-19-related complications [60]. A comprehensive study within the health system in New York, involving a cohort of 1,934,294 patients, further demonstrated that vaccination significantly reduced the risk of major adverse cardiovascular events (MACE) [61]. Notably, the same hospital system also reported that among patients with heart failure, full vaccination and vaccine-boosted status correlated with a significantly lower incidence of hospitalizations, ICU admissions and mortality compared to those who were partially vaccinated or unvaccinated [62]. The occurrence of breakthrough SARS-CoV-2 infection (BTI) in vaccinated individuals is rising [63,64]. A recent study from US VA hospitals involving 33,940 such individuals, however, showed that individuals with BTI had lower risks of death (HR = 0.66, 95% CI: 0.58, 0.74) and fewer post-acute sequelae compared to 113,474 unvaccinated individuals with SARS-CoV-2 infection [65]. This illustrates that despite the possibility of BTI, vaccination still offers substantial protection against severe outcomes. Further studies are needed to examine the effects of COVID vaccination on the risk of future cardiac events.

3. COVID-19 and the Heart: Future Directions

The COVID-19 pandemic has revealed important lessons in the management of cardiovascular disease [28,66,67]. First, it has emphasized the need for close monitoring and management of cardiovascular conditions in individuals with COVID-19, as they are at increased risk of adverse outcomes. These individuals should receive rigorous clinical evaluation and monitoring to ensure appropriate care. As we have shown in the acute setting, monitoring D-dimer trends may be useful in terms of mortality [5]. Furthermore, those cases of COVID-19 illustrated diverse clinical presentation. Second, the pandemic has underscored the importance of preventive measures, including vaccination, in individuals with pre-existing cardiovascular disease. These measures can help reduce the risk

of severe illness and complications. Third, healthcare systems may need to prioritize and ensure access to critical cardiovascular care for patients during a pandemic. This includes maintaining essential cardiovascular services and providing timely care to prevent adverse outcomes. Lastly, the pandemic has highlighted the importance of public health measures such as wearing masks, practicing good hand hygiene, and maintaining physical distance. These measures can help reduce the transmission of COVID-19 and protect individuals with cardiovascular disease from infection and its potential complications [28].

At the present time, post-acute sequelae of COVID-19 across the spectrum of care settings of the acute infection is lacking. Studies show that increased cardiovascular risks and burdens are present even in individuals who did not require hospitalization during the acute phase of their COVID-19 infection [43]. Our understanding of the underlying mechanism of post-acute sequelae of COVID-19 (long COVID) is currently evolving, leaving global healthcare systems ill prepared to handle the high volume of individuals experiencing cardiorespiratory, neurocognitive, gastrointestinal and musculoskeletal symptoms months and years after contracting acute COVID-19. Vaccination may decrease the chances of developing long COVID, but there are still occurrences of long COVID ensuing from breakthrough infections [65]. Further studies are needed for a more profound understanding of the causes of long COVID.

It is evident that COVID-19 has become endemic and is here to stay. While we have discovered more information, as revealed by current research, there remain many things that we do not know with regard to COVID-19 and its impact on the heart. Therefore, future studies are needed (1) to understand the long-term effects of cardiovascular complications of COVID-19, future cardiovascular events and the impact of mutating variants on cardiovascular complications through data collection and analysis, (2) to identify the most important diagnostic criteria for prognosis of COVID-19 and to understand the disease mechanism through biomarkers and advance cardiac imaging, including echocardiography and (3) to develop novel strategies to manage and treat these cardiovascular complications using the knowledge gained [68].

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