Review Article

COVID-19 and Cardiac Injury: A Complex Interplay

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Abstract

Although the coronavirus disease-2019 (COVID-19) primarily affects the respiratory system, the cardiovascular system is the potential target since angiotensin-converting enzyme 2 (ACE2), which acts as a receptor for the virus, is also extensively expressed in the myocardium. A large proportion of individuals infected with COVID-19 have prior cardiac risk factors in which hypertension and diabetes are the most prevalent comorbidities. Cardiac injury, defined as an elevated cardiac troponin, is the most reported cardiac abnormality in COVID-19. Acute cardiac injury can occur through a number of possible mechanisms include: (1) Non-ischemic myocardial injury related to various causes e.g., systemic inflammation, cytokine storm, stress-induced cardiomyopathy, and myocarditis. (2) Ischemic cardiac injury related to different pathophysiology e.g., plaque rupture, coronary spasm, or myocardial oxygen demand-supply mismatch. Cardiovascular disease and COVID-19 have a complex interplay. The presence of preexisting cardiovascular disease increases susceptibility to COVID-19 infection as well as morbidity and mortality. On the other hand, COVID-19 infection can worsen the underlying cardiovascular disease or even trigger new complications, such as myocardial injury, which is closely related to the disease progression and prognosis.

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Introduction

The case of atypical pneumonia of unknown etiology was first diagnosed in Wuhan, Hubei Province, China on December 8, 2019. A few days later, China reported a cluster of cases of "unexplained pneumonia" to the World Health Organization (WHO), attracting great attention worldwide. A new strain of coronavirus, 2019-nCoV (2019 novel coronavirus) which was later renamed as SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), was identified as the cause on January 9, 2020. On January 13, 2020, the first case outside China was reported in Thailand. Soon after that, WHO declared coronavirus disease-2019 (COVID-19) a pandemic on March 11, 2020, due to the growing number of reported cases worldwide.[1, 2]

The SARS-CoV-2 belongs to the same family as SARS-CoV (severe acute respiratory syndrome coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) which caused previous outbreaks in China in 2002[3] and Saudi Arabia in 2012,[4] respectively. SARS-CoV-2 has higher transmissibility than SARS-CoV making it difficult to control the widespread outbreak. The patients can present as either symptomatic or asymptomatic. The common presenting symptoms in a cohort of 41 patients from Wuhan were fever (98%), cough (76%), dyspnea (55%), and myalgia /fatigue (44%). Less common symptoms were sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%).[5]

Although respiratory tract infection is the main clinical manifestation of COVID-19, variable extrapulmonary involvements, including the cardiovascular system, can occur. While acute respiratory distress syndrome (ARDS) is the most common complication of COVID-19,[6] the heart is the earliest damaged organ after the lungs.[7] The cardiovascular impact of SARS-CoV-2 seems more prominent than SAR-CoV and MERS-CoV and were correlated with disease severity.[8]

This review aims to explain the interplay of COVID-19 and pre-existing cardiovascular disease including the common presence of underlying cardiovascular conditions and the potential mechanism of cardiac injury as an acute consequence of COVID-19.

Prevalence of Cardiovascular Disease in COVID-19 Patients

Coronaviruses can affect the cardiovascular system in individuals with or without underlying cardiovascular disease (CVD). Nevertheless, data suggest that a large proportion of patients have prior cardiovascular disease and/or risk factors. According to the data released by the National Health Commission of China, 35% of patients with COVID-19 had a history of hypertension and 17% had a history of coronary heart disease.[9] In a meta-analysis including 1,576 infected patients, the most prevalent comorbidities were hypertension (21.1%), followed by diabetes (9.7%), CVD (8.4%), and respiratory tract disease (1.5%).[10]

COVID-19 Outcomes Amongst Patients with Pre-existing Cardiovascular Disease

Numbers of studies suggest the association of preexisting CVD and the severity of COVID-19 infection. In a meta-analysis from China including 1,527 COVID-19 patients, the presence of hypertension, cardiovascular diseases, and diabetes were 2-fold, 3-fold, and 2-fold, respectively, higher, in patients with severe disease or requiring ICU admission. Another important finding was the damage the SARS-CoV-2 did to the heart. At least 8% of patients with COVID-19 experienced acute cardiac injury and the incidence is about 13-fold higher in patients with severe disease treated in ICU.[11] In the largest case series to date which included 44,672 confirmed COVID-19 cases from Wuhan, China, pre-existing comorbidities that were predictors of high mortality included CVD (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%), and cancer (5.6%), compared to the overall mortality rate of 2.3%.[1]

The exact mechanism underlying the association between CVD and COVID-19 severity has not been entirely understood and various possible mechanisms are speculated. COVID-19 may decompensate preexisting CVD or trigger de novo cardiovascular complications. On the other hand, CVD is associated with advanced age. Age is both a risk factor for CVD and COVID-19 mortality[12] as aging weakens the immune system making the body more vulnerable to COVID-19. The observed correlation between CVD, hypertension, and diabetes with adverse outcomes in COVID-19 may be a reflection of the higher

incidence of these comorbidities with advanced age.[13]

SARS- CoV-2, Angiotensin-converting Enzyme-2 and Target Organs

SARS-CoV-2 enters the host cell through binding the spike protein with angiotensin-converting enzyme 2 (ACE2) which serves as the primary receptor for both coronaviruses to gain entry into the cells. However, SARS-CoV-2 has a higher binding affinity for ACE2 than SARS-CoV[14] which explains its higher transmission potential. In addition to the lungs, many human organs are rich in ACE2 receptor e.g. the heart, endothelium, oral and nasal mucosa, thymus, spleen, liver, kidneys, nervous system, adipose tissue, and gastrointestinal system which can be easily infected.[15]

Patients with cardiovascular comorbidities e.g. heart failure, diabetes, and hypertension may be prone to COVID-19 infection due to the upregulation of ACE2.[16] It has been reported that Angiotensin-converting enzyme inhibitors (ACEIs) or Angiotensin II receptor blockers (ARBs) increase ACE2 expression in mice.[17] However, there is no supporting evidence that ACEIs and ARBs increase SARS-CoV-2 infection. Based on the current evidence, all published guidelines and statements from professional societies suggest continuing the previously prescribed ACEIs/ARBs. On the other hand, the start of renin–angiotensin–aldosterone-system antagonist is not recommended in the patient without clinical indication owing to the lack of evidence showing the benefit of these medications in COVID-19 patients to date.[18-26]

Cardiac Injury

The most frequently reported cardiovascular complication in COVID-19 is acute myocardial injury with the overall prevalence ranging from 5 to 38 % and the crude prevalence of 21.4%.[18] Regardless of the true prevalence, acute cardiac injury has been constantly shown to correlate with poor outcomes in COVID-19.[27] In the study by Shi et al,[28] among 416 patients infected with COVID-19, in-hospital cardiac injury occurred in 19.7%. COVID-19 patients who developed cardiac injury tended to have higher incidence of ARDS (58.5% vs 14.7%; $P < .001$) , acute kidney injury (8.5% vs 0.3% ; $P < .001$) and mortality rate (51.2% vs 4.5% ; $P < .001$) than patients without cardiac injury. Multivariable analysis showed that both cardiac injury and ARDS were significantly and independently a predictor of mortality in COVID-19.

Definition of Myocardial Injury

As specified by the 4th Universal Definition of myocardial infarction, the elevation of cardiac troponin (cTn) values above 99th percentile URL is defined as myocardial injury. The injury is considered acute if the rise and /or fall (dynamic change) of cTn values are evidenced.[29] However, many studies on COVID-19 have used various definitions of acute myocardial injury. Many researchers adopted the single time point measurement and did not use high sensitivity cardiac troponin (hs-cTn) assay. Thus, reported cases of acute myocardial injury from COVID-19 likely underestimate its true prevalence.

Pathophysiology of Acute Myocardial Injury

The pathophysiology of cardiac injury from COVID-19 have not been fully understood and might be multifactorial. Listed below are the possible mechanisms of cardiac injury in the setting of COVID-19.[18, 30]

1. Myocardial oxygen demand and supply mismatch:

A sudden increase in myocardial oxygen demand from systemic inflammation, tachycardia, along with a decrease in oxygen supply to the myocardium from hypotension or hypoxemia from respiratory failure can cause type 2 myocardial infarction.

2. Acute coronary syndrome:

Plaque rupture may be precipitated by systemic inflammation leading to type 1 myocardial infarction

3. Microvascular dysfunction:

Host inflammatory response and hypercoagulability can cause microvascular thrombosis and endothelial injury

4. Stress-induced cardiomyopathy:

Both physical, psychological, or socio-economic stress (lock down, economic downturn, loss of job, etc.) related to the pandemic can be the triggering factors for the development of stress-induced cardiomyopathy

5. Systemic inflammation:

Severe COVID-19 can induce inordinate

production of cytokine so-called cytokine storm, which lead to multiple organ injury and depressed myocardial function.

6. Direct viral infection of cardiomyocyte and myocarditis:

Direct infection of cardiomyocyte may be possible due to the presence of ACE2 on the myocardial cell which may result in cell damage. Tavassi et al[31] published a case report of a COVID-19 patient with myocarditis-like symptom and cardiogenic shock with endomyocardial biopsy showing viral particle identical to SARS-CoV2 in the heart. However, the viral particles were identified in the interstitial macrophage and their surrounding but not in the cardiac myocyte. This suggests that the heart can be directly involved by SARS-CoV-2 but do not provide the evidence of direct cardiomyocyte invasion.[31, 32]

Interaction Between Cardiovascular Comorbidity and Myocardial Injury in COVID-19

According to recent research about the relation between COVID-19 and underlying Cardiovascular Disease by Guo et al,[33] the sample size was 187 hospitalized patients, 35.3% of whom had CVD (hypertension, coronary artery disease, or cardiomyopathy) and 27.8% had developed myocardial injury specified by the elevated cTnT. The mortality rate was 7.62% among participants with normal cTnT levels without underlying CVD, 13.33% with normal cTnT levels with underlying CVD, 37.5% with elevated cTnT levels without underlying CVD, and 69.44% with elevated cTnT levels with underlying CVD. These findings suggested that the co-presence of CVD and myocardial injury was associated with the worst prognosis while the prognosis of participants with underlying CVD but without myocardial injury appeared relatively favorable. Another finding is that the use of renin-angiotensin-aldosterone-system antagonists in the patient who had cTnT elevation was not considered to have an effect on the mortality rate.[34]

Classification of Myocardial Injury

Myocardial injury can be either acute or chronic and occurs due to an ischemic or non-ischemic process. The injury is considered acute if there is a dynamic change in the cTn levels and chronic if there is a stable level of elevated cTn (≤ 20% variation). The classification and potential mechanisms of myocardial injury in COVID-19 are illustrated in Figure 1.[29,35]

Chronic Myocardial Injury

Chronic myocardial injury characterizes by a stable level of elevated cTn or the value could be varied within 20%. Prevalence of chronic cardiovascular conditions such as structural heart disease,

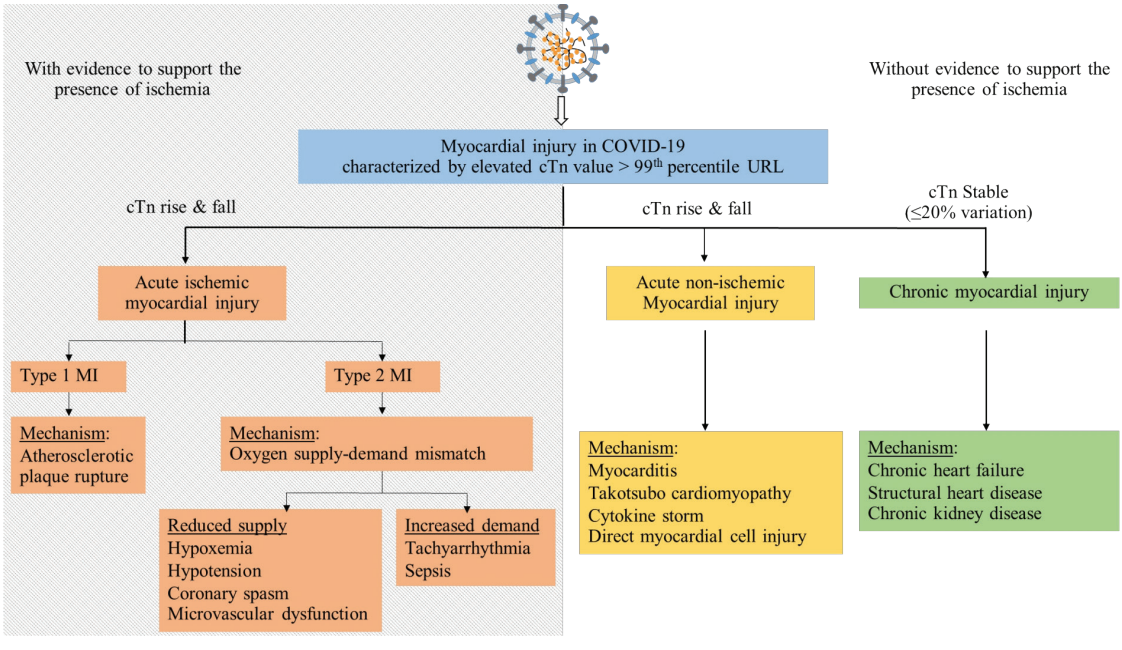

Figure 1 Classification of myocardial injury in COVID-19 according to mechanism (modified from Sandoval Y et al, and Thygesen K et al.).

chronic heart failure, cardiomyopathy, or chronic kidney disease tends to be the explanation for the presence of myocardial injury in the COVID-19 setting.

Acute Ischemic Myocardial Injury

Type 1 MI

Previous research had found a significant association between respiratory infections, especially influenza, and acute myocardial infarction.[36] The action of the immune system against COVID-19 leads to systemic inflammatory response and hemodynamic changes. These reactions result in a theoretically increased chance of atherosclerotic plaque rupture or thrombus formation and able to develop ST-Elevation Myocardial Infarction or non-ST-segment elevation acute coronary syndrome as a consequence. However, the incidence of ST-elevation associated with COVID-19 is still unexplored to date.

Type 2 MI

Severe COVID-19 pneumonia can induce tachycardia, hypoxemia, or hypotension. The mismatch of myocardial oxygen demand and supply may occur and if this imbalance condition is still pronounced and sustained, it can contribute to type 2 MI. The incidence was higher when underlying coronary artery disease exists.[35,37]

Acute Non-ischemic Myocardial Injury

Various mechanisms can lead to acute non-ischemic myocardial injury. Myocarditis and stress-induced cardiomyopathy are among the common etiologies.

Myocarditis

Myocarditis is an inflammatory cardiac disorder characterized by inflammatory cellular infiltrate and myocyte injury without ischemic cause. The clinical manifestations range from asymptomatic to fulminant myocarditis and cardiogenic shock. It has been proposed that the combination of direct virus-induced cell injury and immune response secondary to the virus, plays a major role in the destruction of myocardial cells.[38,39] The true prevalence of myocarditis among COVID-19 patients is not known because endomyocardial biopsy is rarely performed due to the risk of infection. Cardiac magnetic resonance imaging (CMR) can be helpful in the diagnosis of myocarditis but, again, it was difficult to perform in highly infectious patients.[40]

Stress-induced Cardiomyopathy

Stress-induced cardiomyopathy or Takotsubo cardiomyopathy is a clinical syndrome characterized by acute and transient regional wall motion abnormality of the left ventricle in the absence of significant obstructive coronary artery disease.[41] It is typically precipitated by intense emotional or physical stress. A typical case of stress-induced cardiomyopathy in a patient with acute myocardial injury triggered by SARS-CoV-2 infection has been reported by Meyer et al.[42] Another report from Sala et al[43] described a COVID-19 patient who developed LV systolic dysfunction with a pattern of reverse Takotsubo cardiomyopathy, which hypokinesia occurred in basal and mid left ventricular segments instead of apical part.

Myocardial Injury with Cytokine Storm

Cytokine storm also known as "hypercytokinemia" or "cytokine release syndrome" is a phenomenon that represents a hyperactive immune response characterized by the release of proinflammatory cytokines.[44] This exact phenomenon has also been reported in SARS, MERS, and influenza patients.[12] In COVID-19-induced cytokine storm, the plasma level of interleukin (IL)-1β, IL-6, interferon gamma inducible protein (IP)-10, tumor necrosis factor (TNF), interferon-γ, macrophage inflammatory protein (MIP) -1α, MIP -1β, and vascular endothelial growth factor (VEGF) has been found to be elevated.[45] Among these elevated inflammatory mediators, IL-6 which was found to be strongly correlated with disease mortality plays a key role in mediating cytokine storm by stimulating the production of other cytokines, promoting vascular leakage, and finally causing interstitial edema.[44,46] Myocardial injury caused by hyperactivation of immune response was reported by Zhou et al[47] in which 191 hospitalized patients with COVID-19 were enrolled. In this study, increased hs-cTnI levels were detected in 17% of the patients, especially in non-survivors which the level seemed to be rapidly increased from day 13 after the disease onset with

similar trends on inflammatory biomarkers such as d-dimer, serum ferritin, lactate dehydrogenase (LDH), and IL-6.[48] Elevated inflammatory biomarkers together with elevated cardiac enzyme levels suggested that cytokine storm and systemic inflammatory response syndrome (SIRS), rather than direct cardiomyocyte infection, are more likely to be the underlying mechanisms of myocardial damage.[7, 37]

Diagnostic Evaluation

Biomarker for Myocardial Injury in COVID-19

Biomarkers of cardiac injury, such as cTn and brain natriuretic peptide (BNP), have been substantially related with worse clinical outcomes in COVID-19 patients. BNP, which rises immediately following myocardial injury, is found to be well correlated with the size of myocardial injury and associated with risks of both ICU admission and in-hospital mortality. Elevated cTnI/cTnT is associated with ICU admission, in-hospital mortality, and severity of inflammation.[49] Aside from that, the changing patterns are also important. While COVID-19 survivors had stable levels of cTn, non-survivors tended to have higher cTn levels that continued to rise until their deaths.[47] These findings may support the use of serial cTn measurement to identify subsets of patients with evidence of acute myocardial injury who may have a worse prognosis and need further evaluation and special management.[12, 35]

Imaging Test for Myocardial Injury in COVID-19

Acute cardiac injury cannot be diagnosed by using cardiac biomarkers alone as they are found to be elevated in other conditions. Since various mechanisms can lead to cardiac injury, other tools such as ECG and imaging modalities including echocardiography, cardiac magnetic resonance (CMR) imaging, and coronary computed tomography (CT) may help the clinician to establish a diagnosis and clarify underlying etiologies. Abnormal ECG such as ST-segment deviation (elevation or depression), conduction disturbances, and low voltage are found more frequently in patients with myocardial injury. 30.9% of patients with myocardial injury whose baseline ECG was found to be normal at presentation developed new ECG changes during hospitalization. Echocardiography, the often preferred imaging test, was able to detect abnormalities in nearly two-thirds of COVID-19-associated myocardial injury patients. Major abnormalities being reported included left ventricular (LV) regional wall motion abnormalities (23.7%), global LV dysfunction (18.4%), grade II and III LV diastolic dysfunction (13.2%), right ventricular (RV) dysfunction (26.3%), and pericardial effusion (7.2%).[50] CMR imaging can help identify the nature of myocardial injury with high accuracy for the diagnosis of acute myocarditis with some limitations in critically ill patients. Coronary CT may be useful for the detection of obstructive CAD. Cardiac catheterization, coronary angiography, and endomyocardial biopsy may add clinical benefits in selected patient but they are considered invasive procedures. Due to the contagious risk of COVID-19, both noninvasive imaging and invasive cardiac procedures should be carefully selected and performed only if the result will affect the management.

Discussion

The COVID-19 outbreak has progressed to a global health emergency with the spectrum of the disease ranging from asymptomatic to severe pneumonia and ARDS. The presence of hypertension, cardiovascular diseases, and diabetes are associated with a greater risk of severe disease. Many observational studies have found a significantly increased mortality rate in COVID-19 patients who have preexisting cardiovascular comorbidities. However, the association between the worse outcome in COVID-19 and cardiovascular comorbidities is not unique as many infections are also made worse by the underlying cardiovascular disorder. Growing evidence indicates that cardiac involvement is seen in COVID-19 and appears to be more common compared with the previous SARS-CoV infection. Acute cardiac injury is the most commonly described cardiovascular complication. The mechanism of cardiac injury, as defined by an increased cTn level, can be explained by myocardial ischemia and non-ischemic cause of injury which is more common. The presence of cardiac injury is significantly associated with the worse outcome of COVID-19, while the prognosis

of patients with underlying cardiovascular disease but without myocardial injury is relatively favorable. The exact pathophysiology of acute myocardial injury is not clearly understood. Based on the available evidence, myocardial injury seems to be largely attributable to the hyperinflammatory state, cytokine storm, and increased cardiac stress due to respiratory failure and hypoxemia. It remains controversial as to whether SARS-CoV-2 directly infects myocardial cells causing myocardial cell damage and viral myocarditis. At present, there is limited evidence on the definite diagnosis of myocarditis caused by SARS-CoV-2, and no histological evidence of direct infection of SARS-CoV-2 in the myocardium was reported to date.

The relationship between cardiovascular comorbidity and COVID-19 is bidirectional. Patients with preexisting cardiovascular comorbidities may face a greater risk of developing into severe illness and are at high risk for morbidity and mortality. On the other hand, COVID-19 can, in turn, cause cardiac injury which is closely related to the disease progression and prognosis. Considering this, the complex interplay of cardiac injury and COVID-19 should be taken into account in clinical practice. Finally, further research on the interaction of COVID-19 on the cardiovascular system is essential and clinicians have to be aware of the potential cardiovascular complication that can occur during the course of COVID-19.

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