Dilated Cardiomyopathy Risk in Patients with Coronavirus Disease 2019: How to Identify and Characterise it Early?

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Abstract

Multiple lines of evidence have shown that elevated blood troponin is strongly associated with poor prognosis in patients with the novel coronavirus disease 2019 (COVID-19). Possible mechanisms of myocardial injury in COVID-19 include ischaemia due to circulatory and respiratory failure, epicardial or intramyocardial small coronary artery thrombotic obstruction due to increased coagulability, and myocarditis caused by systemic inflammation or direct binding of the virus to its receptor, angiotensin-converting enzyme-2 (ACE2), which is abundantly expressed in the heart. It is postulated that persistent immune activation upon viral infection increases the risk of developing dilated cardiomyopathy in COVID-19 patients.

Keywords

COVID-19, SARS-CoV-2, myocardial injury, troponin, myocarditis, cardiomyopathy, heart failure

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The novel coronavirus disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a public health emergency of international concern.[1] The pandemic is ongoing, and the world is faced with the urgent task of minimising the mortality associated with COVID-19. Besides advanced age, risk factors for escalation of COVID-19 severity include underlying comorbidities, such as cardiovascular disease, diabetes, malignant neoplasm and chronic respiratory disease.[2,3] Limited information is available on cardiac complications that can lead to fatal outcomes in patients with COVID-19. However, an increasing number of reports have shown that direct and indirect effects of SARS-CoV-2 on the heart are extremely important as prognostic determinants of COVID-19.[5–7]

Angiotensin-converting enzyme-2 (ACE2) is a membrane-associated aminopeptidase that inhibits the activation of the renin–angiotensin system and prevents the development of heart failure (HF), hypertension and diabetes.[4] Moreover, ACE2 serves as a functional receptor for SARS-CoV-2, and COVID-19 is triggered by binding of the SARS-CoV-2 spike protein to ACE2. In addition to well-known mucosal epithelial cells in the respiratory tract and alveolar type II epithelial cells, ACE2 is highly expressed on the myocardium and vascular endothelium. Therefore, after entering the body, SARS-CoV-2 can damage the heart and vasculature as well as causing pneumonia.

An increase in blood troponin levels (troponin I or troponin T) is an indicator of myocardial damage, and blood troponin measurements are widely used for the diagnosis of acute coronary syndrome (ACS). Several studies have documented a strong association between COVID-19 progression and elevated blood troponin.[5–7] In hospitalised patients with COVID-19, mortality in the elevated blood troponin group was 51.2–59.6%, a range markedly higher than the 4.5–8.9% in the normal blood troponin group.[5,6] The incidence of lethal arrhythmia increases during follow up in patients with COVID-19 and elevated blood troponin;[3] therefore, patients with COVID-19 and elevated blood troponin should be provided with cardiac function/arrhythmia monitoring (ECG and N-terminal pro-brain natriuretic peptide measurement) during management, and it is important to appropriately triage such patients and design treatment strategies to address specific cardiac conditions. Patients with cardiovascular disease tend to have higher blood troponin levels than those without such disease. Moreover, even in patients without underlying cardiovascular disease, those with elevated blood troponin have a poor prognosis; therefore, an elevation in blood troponin may be a prognostic determinant in hospitalised patients with COVID-19.

Further, elevated blood troponin T is associated with the use of ACE inhibitors/angiotensin II receptor blockers (ACEIs/ARBs; elevated troponin group, 21.1% versus normal troponin group, 5.9%; p=0.002).[5] This association may be attributed to the high number of patients with HF or high blood pressure in the elevated troponin group, and the current data cannot be regarded as evidence for an association between ACEI/ARB use and fatal outcome in patients with COVID-19. ACEIs and ARBs, however, have been shown to have beneficial effects on experimental myocarditis.[8,9] Nevertheless, the possibility that ACEIs/ARBs increase the sensitivity to SARS-CoV-2 cannot be ruled out. Given that HF itself is a risk factor for severe COVID-19, careful follow-up for

COVID-19 is warranted for patients with HF undergoing treatment with any ACEI/ARB.

Information about the mechanism by which SARS-CoV-2 infection causes elevation in blood troponin levels, thereby indicating myocardial damage, remains unknown. Although various mechanisms can be postulated, the possible mechanisms are:

- Ischaemia resulting from decreased myocardial oxygen supply because of respiratory failure/hypoxemia due to pneumonia and circulation insufficiency due to shock/low blood pressure.
- Myocardial damage caused by the cytokine storm induced by the strong release of inflammatory cytokines and chemokines.[10,11]
- ACS due to the destabilisation/rupture of the atherosclerotic plaque or coronary spasm caused by the spread of inflammation to the coronary artery.
- Obstruction of the myocardial small coronary arteries due to inflammation-induced enhancement of coagulation activity.
- Cardiomyocyte damage/viral myocarditis caused by the direct binding of SARS-CoV-2 to cardiomyocytes.

Regarding ACS, 18 patients with COVID-19 were found to have ST elevation on ECG.[12] Nine of these patients were given coronary artery angiography; coronary obstruction was detected in six patients; the remaining three patients were considered to have non-coronary-obstructive myocardial damage. Of the nine patients who did not undergo angiography of the coronary artery, two were diagnosed with MI due to epicardial coronary artery obstruction based on ECG and echocardiography. The remaining seven patients were diagnosed with non-coronary artery-related myocardial injury. Overall, more than half of the patients with COVID-19 and ST elevation on ECG had non-coronary artery-related myocardial injury, and fewer than half of them had MI due to coronary artery thrombus. Thus, myocardial injury unrelated to epicardial coronary artery obstruction is frequent in COVID-19 patients. Moreover, elevated D-dimer levels were observed in all 18 patients, suggesting the relevance of the thrombotic occlusion of epicardial or intra-myocardial small coronary arteries as a mechanism of ST elevation. Nevertheless, 13 of these 18 patients died, and myocardial damage appears to be closely associated with poor prognosis regardless of the presence or absence of coronary obstruction.

Currently, a high frequency of SARS-CoV-2 infection-induced myocarditis has not been observed. However, acute/fulminant myocarditis has been reported in individuals infected with SARS-CoV and Middle East respiratory syndrome CoV.[13] Considering the pathogenic similarities, it can be predicted that SARS-CoV-2 can cause myocardial damage via direct and/or indirect effects.[7] Moreover, growing indirect evidence of high ACE2 expression in the heart and elevated troponin in patients with severe COVID-19 suggests that SARS-CoV-2 infection can induce myocarditis.[13] Although the aetiology of non-hereditary dilated cardiomyopathy has not yet been elucidated, viral genomes have been detected in myocardial tissue samples from patients diagnosed with dilated cardiomyopathy, even when infiltrating inflammatory cells are undetectable.[14] Furthermore, some patients with myocarditis had repeated cycles of recurrence and remission.[14–17] It is presumed that upon viral infection, a persistent immune mechanism is activated, leading to a transition to dilated cardiomyopathy.[15–17] Moreover, potential persistent infection of the heart cannot be ruled out even after SARS-CoV-2 becomes undetectable on polymerase chain reaction of samples collected from the pharyngeal or nasal mucosa. Therefore, for patients whose blood troponin levels are elevated after SARS-CoV-2 infection, long-term careful monitoring of cardiac function is necessary after recovery. Further, studies should address whether conditions such as dilated cardiomyopathy would develop following COVID-19 even when patients are asymptomatic. ■

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