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Elevated Troponin in Patients With Coronavirus Disease 2019: Possible Mechanisms

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a pandemic that has affected more than 1.8 million people worldwide, overwhelmed health care systems owing to the high proportion of critical presentations, and resulted in more than 100,000 deaths. Since the first data analyses in China, elevated cardiac troponin has been noted in a substantial proportion of patients, implicating myocardial injury as a possible pathogenic mechanism contributing to severe illness and mortality. Accordingly, high troponin levels are associated with increased mortality in patients with COVID-19. This brief review explores the available evidence regarding the association between COVID-19 and myocardial injury. (*J Cardiac Fail 2020;26:470−475*)

Key Words: COVID-19, Coronavirus, SARS, Troponin, Myocardial injury, Myocarditis.

In December 2019, a series of pneumonia cases of unknown cause emerged in Wuhan, Hubei, China, with clinical presentations greatly resembling viral pneumonia.[1] Deep sequencing analysis from lower respiratory tract samples indicated a novel coronavirus, which was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

As of April 14, 2020, a total of 1,844,863 cases of SARS-CoV-2 infection and 117,021 deaths have been confirmed by the World Health Organization.[2] The most feared clinical presentation of coronavirus disease 2019 (COVID-19) is bilateral interstitial pneumonia, which may progress to acute respiratory distress syndrome. The latter occurs in approximately 3%−30% of hospitalized patients with COVID-19, depending on the cohort.[1,3−8]

Analyzing the first reports from China, a considerable proportion of patients (12%−28%) presented elevated cardiac troponin levels.[1,6,8,9] Compared with patients with normal levels, those with elevated troponins were older and had significantly higher rates of comorbidities including hypertension, coronary artery disease (CAD), and diabetes.[6] Notably, patients with higher troponin levels were more likely to be admitted to intensive care[1,5] and showed higher in-hospital mortality.[6−8,10−13]

Acute respiratory infections as well as sepsis are often associated with an increase in troponin, which can be used as a marker of disease severity and predicts future cardiovascular events.[14−16] Hypotheses on COVID-19−associated myocardial injury are consistent with previous observations relating to the outbreaks of SARS and Middle East respiratory syndrome. Several mechanisms have been proposed, which are summarized in Figure 1. In this review, we provide an overview of the available evidence regarding the possible mechanisms of myocardial injury in COVID-19.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histologic, immunologic, and immunohistochemical criteria.[17] Many viruses are cardiotropic, meaning that they bind directly on molecular targets in the myocardium. Myocardial damage may be due to different mechanisms. In the initial phase of viral myocarditis, direct virus-mediated lysis of cardiomyocytes occurs.[18] This process is usually followed by a robust T-cell response, which can lead to further heart injury and ventricular dysfunction.[19,20] In COVID-19, particular attention has been given to the role of angiotensin-converting enzyme 2 (ACE2), the binding receptor for SARS-CoV-2 cellular entry.[21] ACE2 is highly expressed in pericytes of adult human hearts, which indicates an intrinsic susceptibility of the heart to SARS-CoV-2 infection.[22] SARS-CoV-2 seems to not only gain initial entry through ACE2, but also to

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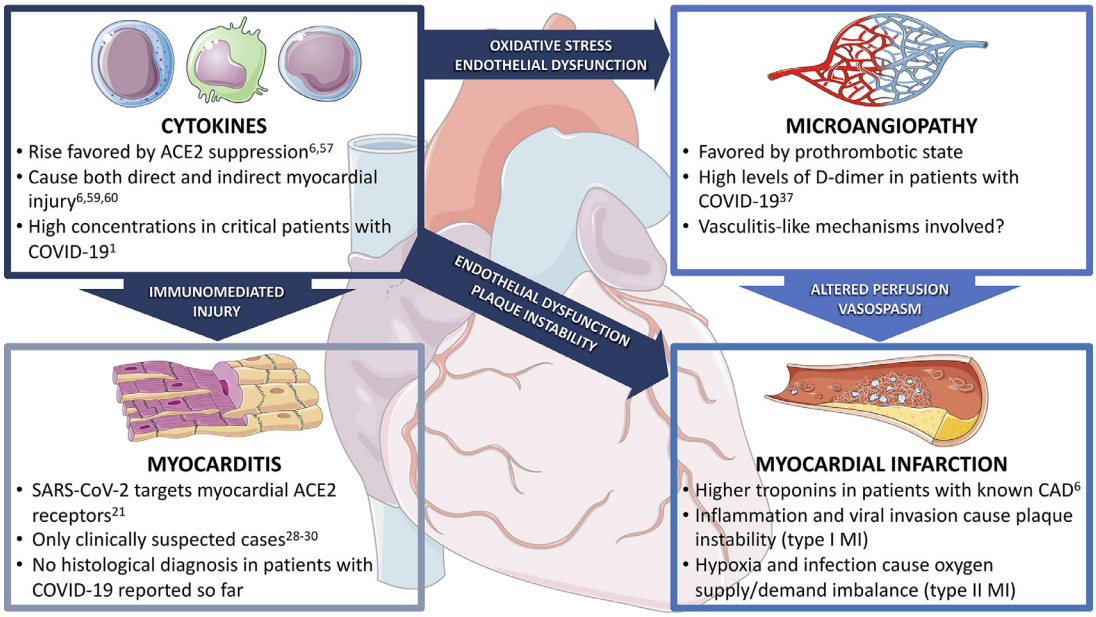

Fig. 1. Possible mechanisms explaining troponin elevation in patients with COVID-19. (Modified from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/). ACE2, angiotensin-converting enzyme 2; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; MI, myocardial infarction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

subsequently downregulate ACE2 expression, resulting in reduced conversion of angiotensin II (Ang-II) to angiotensin 1−7 (Ang-1−7). Ang-1−7 physiologically mediates protective cardiovascular effects in target organs.[23,24]

In autopsies of patients who died from the SARS outbreak in 2002, 35% of heart samples showed the presence of viral RNA in the myocardium, which in turn was associated with reduced ACE2 protein expression.[25] SARS-CoV-2 may share the same mechanism with the first SARS coronavirus because the 2 viruses are highly homologous in genome.[6,26,27] The consequences of ACE2 downregulation on the cardiovascular system is further expanded on.

Myocarditis represents one of the most challenging diagnoses in cardiology. Suspicion rises with the number of criteria fulfilled.[17] However, diagnostic certainty is based on endomyocardial biopsy or autopsy, where histologic analyses (infiltration, lymphocytes, macrophages, cellular inflammatory types) or molecular methods of viral genome identification can be performed.

To the best of our knowledge, only 3 case reports of probable COVID-19 myocarditis are available to date,[28−30] but none have been proven by biopsy. A fourth case describes the autopsy of a patient with severe COVID-19 who died from sudden cardiac arrest.[31] Interestingly, there were no obvious histologic changes seen in the heart tissue.

The emergency setting of many hospital facilities during the pandemic together with strict hygienic measures intended to prevent further contagion may hinder large studies on biopsy specimens in patients with COVID-19 and the performance of autopsies. At present, no convincing evidence of histologically confirmed COVID-19 myocarditis has been published.

Microangiopathy

SARS-CoV-2 uses ACE2 as its entry receptor, and subsequently downregulates ACE2 expression. In addition to the heart and lung, ACE2 is localized in the intestinal epithelium, vascular endothelium, and the kidneys.[32,33] In the renin−angiotensin−aldosterone system, ACE2 catalyzes the conversion of Ang-II to Ang-1−7, which opposes the vasoconstrictor, proinflammatory, pro-oxidant, proproliferative, and profibrotic actions exerted by Ang-II via AT1 receptors.[34] As a result, suppression of ACE2 expression and subsequent increase in Ang-II[35] levels may represent another threat to heart and vessels in patients with COVID-19. However, the role of Ang-II/Ang-1−7 imbalance in COVID-19 is extrapolated based on limited data from a different, albeit closely related, coronavirus (SARS-CoV).

The clinical significance of this pathway in COVID-19 complications and any possible role of modulating this receptor are not yet fully known. A clinical trial testing recombinant human ACE2 as a treatment for patients with COVID-19 is currently ongoing (NCT04335136). This drug may play a double role, both by acting as a decoy and competitively decreasing viral cell entry, and by restoring ACE2 activity and its beneficial role.[36]

Endothelial dysfunction, cytokine storm, oxidative stress, and Ang-II upregulation may explain the coagulopathy frequently seen in severe coronavirus disease.[37] A postmortem study from Singapore[38] on patients with SARS reported that 4 of 8 patients had pulmonary thromboembolic lesions and 3 patients had deep vein thrombosis. To date, there is only 1 described case of COVID-19−associated pulmonary embolism,[39] but approximately one-half of patients with

COVID-19 present high levels of D-dimer,[3] which is associated to disease severity and higher mortality.[40] This marked increase in D-dimer may be due to intense inflammation stimulating intrinsic fibrinolysis in the lungs with spillover into the bloodstream.[41]

Another factor that may contribute to microangiopathy is vasculitis. Several studies have linked coronavirus infection with Kawasaki disease, especially in children.[42–44] Furthermore, a case series of 3 deceased SARS patients in 2003 described findings of systemic vasculitis, including edema, localized fibrinoid necrosis, and infiltration of monocytes, lymphocytes, and plasma cells into vessel walls in the heart, lung, liver, kidney, adrenal gland, and the stroma of striated muscles.[45] It has been suggested that, in patients with COVID-19, microvascular damage occurring in the heart causes perfusion defects, vessel hyperpermeability, and vasospasm, leading to myocardial injury.[46,47] Notably, a considerable proportion of critically ill patients with COVID-19 present with acute kidney injury, which is associated with worse prognosis.[8,48] The mechanism may be the same, with microangiopathy of renal vessels, but there is no strong supporting evidence to date. Worsening of troponin clearance in patients with acute kidney injury could also contribute to the elevated levels in those patients.

Myocardial Infarction

Patients with preexisting CAD and those with risk factors for atherosclerotic cardiovascular disease (CVD) are at an increased risk of developing an acute coronary syndrome during acute infections, as demonstrated previously in epidemiologic and clinical studies of influenza[49–51] and other acute inflammatory conditions.[52] This outcome could result from imbalance between oxygen supply and demand in the acute setting, so that the troponin elevation may be interpreted as a type 2 myocardial infarction (MI).[53] Reduced oxygen supply in patients with COVID-19 is typically caused by hypoxic respiratory failure, a feature that is more common in deceased patients than in patients who recover[10] and is a marker of disease severity.[9] In contrast, infectious states are often accompanied by fever, tachycardia, and endocrine dysregulation, which lead to a marked increase in myocardial oxygen demand. Moreover, hypoxemia also leads to excessive intracellular calcium with consequent cardiac myocyte apoptosis.[47]

By definition, a type 2 MI can occur with or without underlying CAD. However, considering the higher prevalence of elevated troponin in patients with COVID-19 with previous CVD, it is possible that the type 2 MI when underlying stable coronary disease is unmasked by the acute infection.

Type 1 MI, caused by plaque rupture with thrombus formation, may also be precipitated by COVID-19.[53] Circulating cytokines released during a severe systemic inflammatory stress could lead to atherosclerotic plaque instability and rupture.[54] In addition, the suppression of ACE2 expression and Ang-II increase may elevate cardiovascular risk through mechanisms such as oxidative stress, endothelial dysfunction, and vasoconstriction. Moreover, because ACE2 is expressed in vascular endothelial cells,[32,33] direct viral vascular infection leading to plaque instability may also play a role in type 1 MI in patients with COVID-19.

The occurrence of acute coronary syndrome and MI in infected patients during the first SARS outbreak has been described.[38,55] However, there are very scarce data about symptoms and electrocardiogram changes related to MI in COVID-19. Chest pain has been broadly reported and is also associated with cardiac injury,[7] but it has a very low specificity owing to the primary lung disease (ie, pleuritic pain). Interestingly, Guo et al[6] reported that on admission no patients showed evidence of acute MI. No data regarding electrocardiogram changes on larger groups have been published to date.

Cytokine Storm

Severe lung inflammation and impaired pulmonary gas exchange in COVID-19 has been suggested to be due to upregulation of proinflammatory cytokines.[56] In healthy subjects, Ang-1−7 limits the synthesis of proinflammatory and profibrotic cytokines. Thus, downregulation of ACE2 by SARS-CoV-2, with a consequent decrease in Ang-1−7 levels, may magnify the cytokine storm, resulting in an overwhelming inflammatory response.[6,57] Cytokines have been extensively studied in patients with heart failure owing to their role in inflammatory modulation, myocyte stress or stretch, myocyte injury and apoptosis, fibroblast activation, and extracellular matrix remodeling.[58]

In the study by Guo et al,[6] plasma troponin levels had a significant positive linear correlation with plasma high-sensitivity C-reactive protein levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis during the progress of the disease. In addition to their direct effects on cardiomyocytes, high levels of circulating cytokines also lead to functional reprogramming of endothelial cells, endothelial dysfunction, and atherogenesis.[6,59,60] In fact, endothelial cells are thought to play a primary role in the inflammatory response in viral infections.[61]

Thus, systemic inflammatory response with cytokine storm is a plausible cause of myocardial injury in the late phases of disease, usually associated with acute respiratory distress syndrome, multiorgan failure, and mortality. Overall, high cytokine levels may represent the key player of myocardial injury in COVID-19, being related to direct myocardial injury, endothelial dysfunction, destabilization of coronary plaque, and microthrombogenesis.

Future Perspectives

Troponin represents a useful marker of disease progression and prognosis in COVID-19. As noted by Guo et al,[6] the 16% of their patients with underlying CVD but normal troponin levels had a relatively favorable outcome. Therefore, myocardial biomarkers should be evaluated in patients with CVD who develop COVID-19 for risk stratification purposes to potentially lead to earlier and more aggressive interventions.

Numerous therapies have been proposed worldwide to reduce COVID-19–associated morbidity and mortality. Some are antiviral drugs acting directly on SARS-CoV-2, with conflicting results to date.[62] Other ongoing trials are testing immunomodulating agents, aimed at decreasing the excessive inflammatory response that characterizes severe disease progression. Because evidence of inflammatory cell infiltration has been reported in the alveoli of patients with acute respiratory distress syndrome associated with SARS-CoV-2 infection,[31] this finding could justify the use of corticosteroids in patients with COVID-19. Another therapeutic possibility is drugs or biologics that act on the cytokine storm, especially targeting IL-1[63] and IL-6.[64] Further observations on myocardial enzyme curves and imaging studies in patients treated with those drugs are needed to correlate immunomodulation with myocardial protection in COVID-19.

Another important issue in this disease is prevention of thrombotic complications. As noted, severe COVID-19 has been associated with high levels of D-dimer as a marker of a general prothrombotic state.[37] Based on the immunothrombosis model, which highlights a bidirectional relationship between the immune system and thrombin generation, blocking thrombin by heparin may dampen the inflammatory response.[65] Furthermore, heparin also has an anti-inflammatory function, which may be relevant in this setting.[66] Several publications have demonstrated this property and some of the described mechanisms include binding to inflammatory cytokines, inhibition of neutrophil chemotaxis and leukocyte migration, neutralization of the positively charged peptide complement factor C5a, and sequestration of acute phase proteins.[67–70] A systematic review concluded that, in the clinical setting, heparin can decrease the level of inflammatory biomarkers but stressed the need for more data from larger studies.[71]

Conclusions

Elevated troponin levels are frequent in patients with COVID-19 and significantly associated with fatal outcomes. Several mechanisms may explain this phenomenon: viral myocarditis, cytokine-driven myocardial damage, microangiopathy, and unmasked CAD.

At present, none of these mechanisms have been definitely proven to be the main driver of troponin elevation and/or myocardial damage in patients with COVID-19. However, we posit that, although COVID-19 initially presents as a primarily respiratory condition, it quickly involves the cardiovascular system through an imbalance of the renin–angiotensin–aldosterone system mediated by ACE2 depletion. This mechanism may complicate the clinical course mediated through the inflammatory response, endothelial dysfunction and microvascular damage.

Additional study of these mechanisms is clearly needed and may influence the search for ways to prevent myocardial damage (eg, immunomodulating drugs). Given the impact of myocardial damage in the pathophysiology and prognosis of patients with COVID-19, the inclusion of cardiovascular end points in ongoing drug trials is essential.

It is reasonable to triage patients with COVID-19 according to the presence of underlying CVD and evidence of myocardial injury for prioritized treatment and even more aggressive treatment strategies in an effort to decrease mortality.

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