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COVID-19 and Myocardium

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ABSTRACT

Context: The COVID-19 pandemic has involved several millions of people around the world and has dragged thousands of individuals to death. Unfortunately, it seems to be unstoppable for the near future. This review aimed to have a comprehensive appraisal on the latest studies conducted on different aspects of myocardial injury related to COVID-19.

Evidence Acquisition: The researchers searched for accredited international investigations, whether original, review, letters, or commentaries or any other published data, in Pubmed/Medline, Google Scholar, Web of Science, Wiley Online Library, and Research Gate databases.

Results: Although the dominant manifestation of the disease was related to the respiratory system, a growing body of evidence has suggested that the cardiovascular system was also a target for SARS-CoV-2. In this regard, myocardium suffered injury by possible direct and indirect mechanisms. Two patterns of myocardial injury were seen particularly in critical cases of COVID-19; presentation with acute myocardial injury and development of myocardial injury with escalation of the viral illness. In the case of myocardial damage, a cascade of life-threatening adverse events will deteriorate the functions of the cardiovascular system as well as other vital organs. Cardiac biomarkers are helpful for early diagnosis of myocardial injury. Hypertension, previous cardiovascular diseases, and diabetes have been considered to be the foremost clinical risk factors in the setting of COVID-19. The jeopardy of arrhythmia, thrombotic complications, acute myocardial infarction, and myocarditis are also anticipated in patients with COVID-19. Thrombolytics have been found to contribute substantially to life-saving treatment regimen.

Conclusions: Cardiovascular damage in terms of myocardial injury has been assigned a considerable share in patients with COVID-19, which is of paramount importance due to the elevation of the fatality rate. While there is no exclusive medication for this viral uninvited guest, much attention should be paid to maintenance of cardiovascular health, which plays a critical role in the battlefield with COVID-19.

1. Context

Corona Virus Disease-19 (COVID-19) pandemic delivered a wake-up call to health authorities in all countries throughout the world, irrespective of their development status. Since the first human coronavirus that was identified in the tracheal tissue in the mid-1960s (1), severe acute respiratory syndrome-coronavirus- 2 (SARS-CoV-2) is the seventh member of known human coronaviruses (2). Coronaviruses have the potential for rapid mutation and recombination (1). SARS-CoV-2 has 82% nucleotide identity with its peer, SARS-CoV, while its similarity to Middle East Respiratory Syndrome Virus (MERS-CoV) is around 50% (1). Remarkable similarities in epidemiologic, clinical, radiologic, and laboratory findings have been documented between SARS-CoV and SARS-CoV-2 infections (3).

The entrance of SARS-CoV-2 into the host cells is through a zinc peptidase, Angiotensin Converting Enzyme 2 (ACE2), which is expressed on the surface of the endothelial cells of the vessels as well as arterial smooth muscles, respiratory tract epithelium, and immune cells (4-6). Fever, cough, and shortness of breath as the main symptoms of COVID-19 are sometimes accompanied with muscle pain, anorexia, malaise, sore throat, nasal congestion, dyspnea, and headache (7). Interestingly, the viral load has been detected to be similar in asymptomatic and symptomatic patients

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with COVID-19 (1). Hence, asymptomatic individuals are not distinguishable from clean ones, which helps the virus to be easily transmitted among the population. However, the intensity of symptoms is increased concordance to the increased viral load (8). Searching for the underlying reasons for the differences in the clinical appearance with the same viral dose merits discussion; of course, it is out of the scope of this paper.

With regard to cardiovascular manifestations, COVID-19 has been reported to be associated with an array of cardiovascular disorders, including myocardial injury, myocarditis, acute myocardial infarction, heart failure, dysrhythmia, and venous thromboembolic events (9). In the present study, a comprehensive appraisal of the latest studies on different aspects of the impact of SARS-CoV-2 on myocardium was performed.

2. Evidence Acquisition

The data were retrieved from accredited papers published in Pubmed/Medline, Google Scholar, Web of Science, Wiley Online Library, and Research Gate databases. Different types of articles including but not limited to original studies, narrative or systematic studies, letters to editors, commentaries, and case reports were collected. The used keywords included "myocardial injury", "cardiovascular injury", "myocardial infarction", "cardiovascular manifestations", and their combination with "COVID-19".

3. Results

3.1. Mechanisms of Myocardial Damage by SARS-CoV-2

The mechanisms of myocardial damage by SARS-CoV-2 could be classified into two distinct categories (10) (Figure 1). Considering the first category, direct, 1) given that ACE2 as the pathway of SARS-CoV-2 into the host cells is present on the surface of cardiac cells, its entrance and proliferation into the myocardium is plausible. This viral overload burden possibly deteriorates the normal function of cardiomyocytes. 2) Involvement of ACE2 receptors with SARS-CoV2 may restrict the capacity of angiotensin II breakdown and, consequently, a cascade of ominous events leading to cardiovascular damage is commenced.

Considering the second category, indirect, 1) cytokine storm and systemic inflammation provoked by SARS-CoV-2, which is evidenced in circulating proinflammatory agents, provide suitable substrate for cardiovascular injuries and even organ failure (8, 11). 2) Increased oxygen demand due to infection on one hand and hypoxia because of respiration inefficiency on the other hand impose a cardiometabolic imbalance, which can lead to worse clinical outcomes like Acute Myocardial Infarction (AMI) (10). 3) AMI can originate from another mechanism, too. Systemic inflammation precipitates cardiovascular apparatus for higher blood supply. In this respect, coronary arteries go under increased pressure, which may result in the rupture and erosion of atherosclerotic plaques, jeopardizing the patients to thrombosis-related complications. 4) The medications used to control SARS-CoV-2 infection, like some antiviral drugs, have adverse effects on the cardiovascular system. 5) Any illness may perturb electrolyte imbalance. This situation becomes severe especially in the case of underlying cardiovascular malfunction, which in turn facilitates the emergence of arrhythmias. Due to the interaction of SARS-CoV-2 with Renin-Angiotensin-Aldosterone (RAS) system, hypokalemia is of paramount importance because it makes patients susceptible to various tachyarrhythmias (12).

All aforementioned mechanisms have the potential to injure the myocardium. It seems that systemic inflammation contributes significantly to myocardial injury (10). The close association between troponin T levels and plasma high-sensitivity C-reactive protein is a sign, which shows that myocardial injury and inflammatory states are intertwined reactions (13). A novel study also revealed the presence of viral genome in the heart tissue, substantiating the direct action of SARS-CoV-2 on myocytes (10).

3.2. Laboratory Findings

Myocardial injury makes cardiac biomarkers imbalanced in the serum (9). Acute myocardial injury manifesting in elevated high-sensitive troponin I was reported in 12% of patients with COVID-19 (11). Additionally, two cohorts on hospitalized patients with COVID-19 indicated the elevation

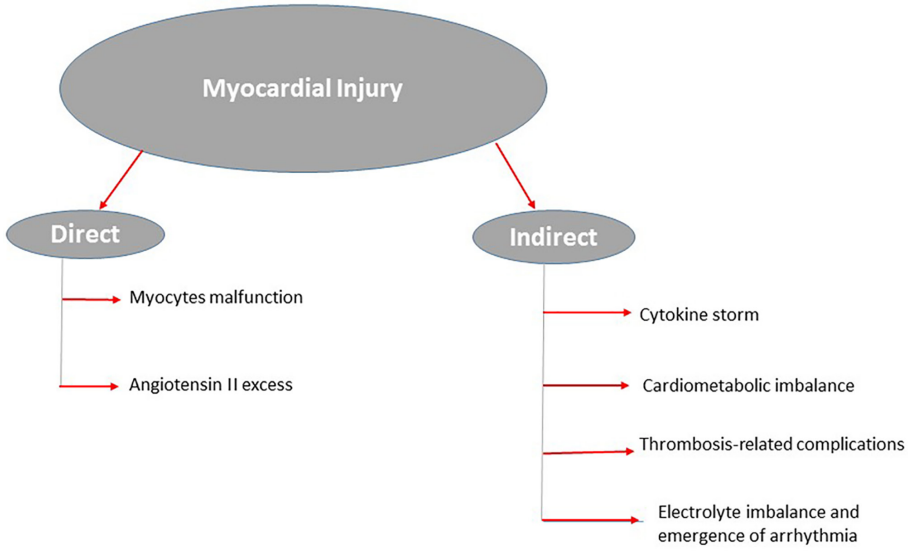

Figure 1. Mechanisms of Myocardial Injury by SARS-CoV-2

of troponin levels, either I or T (13, 14). Moreover, troponin T, creatinine kinase myocardial band test, and N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) that are the indicators of myocardial injury were claimed to be increased in COVID-19 patients (1). The concordant elevation of troponin T level, C-reactive protein, and NT-proBNP shows that there is a causation among myocardial injury, systemic inflammation, and ventricular dysfunction (15). In this context, the biomarkers of systemic inflammation (leukocyte count, C-reactive protein, and procalcitonin) and myocardial injury (creatine kinase, myoglobin, and NT-proBNP) were both increased concurrently in patients with COVID-19 (15). This observation is in line with the previously mentioned statement and corroborates the remarkable role of COVID-19- induced systemic inflammation in myocardial injury. It is believed that altered cardiac biomarkers due to myocardial injury originate mainly from myocarditis (1). Elevated troponin T level was also associated with low partial pressure of oxygen, lower Pao2/fraction of inspired oxygen, and higher levels of lactic acid (FiO2), which totally translates into a severe respiratory illness (13). In addition, higher levels of creatinine and aspartate aminotransferase were seen in companion with higher troponin T levels (13).

Underlying Cardiovascular Disease (CVD) has been assumed to be the driving force for the elevation of troponin T during infection with SARS-CoV-2 (13). As CVD was usually seen more in older ages, it was revealed that COVID-19 patients with elevated troponin T levels were older than those with normal troponin T levels (13). However, changes in troponin T are not strictly correlated to the existence of CVD. Patients with normal troponin T levels and underlying CVD as well as those with elevated troponin T levels without underlying CVD were among COVID-19 patients (13).

3.3. Clinical Risk Factors

In MERS infection, diabetes, hypertension, underlying CVD, and obesity had the highest share among the clinical risk factors for mortality (16). Older age (especially more than 60 years), CVD, diabetes, and cancer were considered as strong predictors of poor clinical outcomes and mortality in SARS-CoV infection (17). In SARS-CoV-2, myocardial injury was likely to be detected in older patients possibly due to the existence of comorbidities like hypertension, coronary artery disease, heart failure, and diabetes (15). Older patients, especially those with CVD, were in need of receiving intensive care due to their greater risk of severe COVID-19 (15). In fact, preexisting CVD makes COVID-19 patients vulnerable to adverse sequels and even death (11, 18-21). A meta-analysis on COVID-19 patients demonstrated that a significant portion suffered from hypertension and cardiac disease (14). In another study on 44672 COVID-19 patients, hypertension had a more prominent role than CVD as the foremost comorbid conditions (22). Cardiac injury was also reported in 19.7% of hospitalized patients with COVID-19. They were significantly older, hypertensive, or diabetic and had a previous history of coronary heart disease, heart failure, or cancer (14). Conspicuously, receiving intense care and worse clinical outcomes were more probable in these high-risk individuals (14). A recent meta-analysis corroborated hypertension, diabetes, and CVD as three prevalent comorbidities that made COVID-19 patients vulnerable to worse clinical outcomes (23) (Figure 2). Nonetheless, there are several reports on hospitalization and death of younger adults (15).

3.4. Clinical Manifestation

Up to now, the dominant clinical manifestation of COVID-19 has been believed to be related to the respiratory system, albeit with varying degrees from mild to lethal (10). Abnormal chest computed tomography was evidenced in at least 85% of the patients. Additionally, about 75% of them had lung involvement in terms of ground-glass opacity and consolidation in subpleural and peripheral areas at both sides (24). Clinical cardiovascular manifestations in COVID-19 patients could be chest pain, dyspnea, dysrhythmia, and acute left ventricular dysfunction (11, 20, 21, 25, 26). Yet, EKG findings could be diverse in patients with COVID-19, which could be misdiagnosed with acute coronary syndrome in some cases (9). Cardiac injury (elevated high sensitivity Troponin I level and electrocardiography or echocardiography abnormalities) was confirmed in 7.2% of all patients and 22% of the cases in the intensive care unit (9). Overall, any remarkable finding in the areas of electro- and echocardiography predicted worse outcomes (13, 14, 27).

Respiratory involvement together with viral infection in extrapulmonary organs and escalation in heart demand precipitate the myocardium under a grave pressure, which may result in acute coronary events (15). The incidence of acute coronary syndrome and myocardial infarction were reported in patients with SARS infection (28, 29). Thrombosis-related complications in terms of pulmonary thromboembolism, deep vein thrombosis, and subendocardial infarction pertinent to occlusive coronary disease were also seen in dead patients due to SARS (28).

Acute myocardial injury has been reported to be the

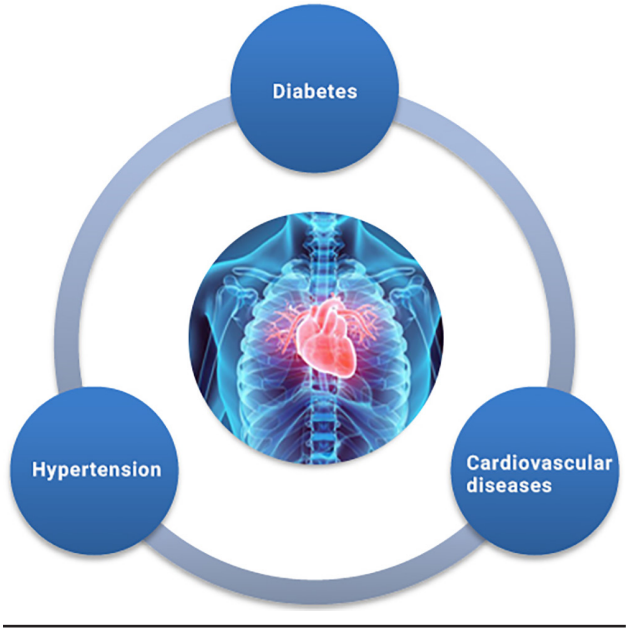

Figure 2. The Most Important Comorbidities Which Intensify Myocardial Injury during Covid-19 Pandemic

most common damage resulting from COVID-19 in the cardiovascular system. The incidence of acute myocardial injury was described variably from 8% to 17% based on the final clinical outcomes (26, 30, 31). Arrhythmia and acute myocardial injury were detected in 16.7% and 7.2% of the hospitalized patients with COVID-19, respectively (20). Viral myocarditis and stress cardiomyopathy were considered as myocardial injury in COVID-19 patients (32). Severe myocarditis with reduced systolic function was reported in patients with COVID-19, as well (8, 33). In a survey on 1099 COVID-19 patients including both hospitalized individuals and outpatients, acute respiratory distress syndrome and septic shock were claimed to be the most common significant manifestations (19). It is logically acceptable that COVID-19 patients whose cardiovascular system does not work properly are vulnerable to the sequels of viral infection. Additionally, complications such as acute respiratory distress syndrome and malignant arrhythmias including ventricular tachycardia, ventricular fibrillation, acute coagulopathy, and acute kidney injury were more likely to occur in those with elevated troponin T levels (19). In a study on COVID-19 patients, underlying CVD including hypertension, coronary heart disease, and cardiomyopathy were seen in 35.3% of the patients, while a lesser percentage (27.8%) showed myocardial injury (elevated troponin T levels). Of note, none of the patients showed other obvious evidences of malfunction in other organs, even acute myocardial infarction on admission (19). However, cardiovascular alterations, including fulminant myocarditis, increased left ventricular end-diastolic diameter, reduced left ventricular ejection fraction, and elevated troponin I and NT-proBNP levels, were observed in a 63-year-old man without prior overt cardiac history. He was improved after two weeks of pharmacotherapy (34). Intriguingly, elevated troponin levels and cardiac arrest during hospitalization were seen in 12% of the patients without any known CVD (35). Elevated cardiac troponin levels in COVID-19 patients have been assumed to have a non-ischemic origin (36). However, due to the respiratory compromise, the incidence of hypoxia-related injuries, even at the cellular level, is expected in the myocardium or any other oxygen-susceptible organ like the nervous system.

3.5. Treatment

At present, treatment approaches in COVID-19 patients with CVD are still adhered to guideline recommendations with the flagship of antiplatelet agents, β blockers, ACE inhibitors, and statins. In the COVID-19 chaos, statins could blunt the cytokine-derived storm, help stabilize the atherosclerotic plaques, and preclude thromboembolic complications. Given that systemic inflammation and cytokine storm are associated with acute respiratory distress syndrome and fulminant myocarditis, deployment of immunomodulators is likely to be salutary in order to depress hyperinflammation and reduce mortality (1).

The treatment plan framework in COVID-19 patients is not significantly different for the patients with normal troponin T levels and those with elevated troponin T levels as both groups are prescribed with antiviral, antibacterial, glucocorticoid, and respiratory support. However, patients with elevated cardiac troponin received more glucocorticoid medications and mechanical ventilation (13). Furthermore, administration of antithrombolytics like heparin as a preventive strategy is emphasized in the COVID-19 patients who need intensive care (37).

Percutaneous coronary intervention remains the treatment of choice in patients with ST Elevation Myocardial Infarction (STEMI) as well as hemodynamically unstable non-STEMI patients with COVID-19. In stable hemodynamic status, conservative therapy with fibrinolysis is deemed enough (38). Risk-benefit assessment of revascularization therapy against fibrinolysis regimen should be done in COVID-19 patients with STEMI (10). Nonetheless, cardiac injury warns poor prognosis in COVID-19 patients (8, 11, 20, 21).

As it is believed that SARS-CoV-2 enters the host cell through ACE2 receptors, there is concern about the cardiovascular patients who use RAS system inhibitors. RAS inhibitors increase the activity of ACE2 on the host cell surface, consequently smoothing the viral entrance. This possibly makes the viral disease in its severe form. However, there are no confirmed data supporting this theory and there are strong suggestions on behalf of several cardiology societies throughout the world in order to adhere to RAS downregulators, including ACE inhibitors and Angiotensin Receptor Blockers (ARBs), in patients with preexisting cardiovascular disorders (39, 40). Indeed, a study revealed that ACE inhibitors/ARBs had beneficial effects in terms of reduction of pulmonary inflammation and cytokine release in patients with viral pneumonia (41).

Finding effective treatment strategies against COVID-19 mostly relies on the elucidation of mechanism/s of injuries induced by this novel coronavirus followed by using drugs that target critical points in the way of these mechanisms. Until that time, prevention is the only option ahead of the world population, which involves trapping the involved individuals, especially asymptomatic ones, tracing people of close contact with virus resources, and social distancing.

4. Conclusions

Like any other respiratory infection, suboptimal cardiovascular function and existence of cardiovascular risk factors increase the susceptibility to COVID-19. It is not surprising that the COVID-19 patients who have myocardial injury will encounter acute respiratory distress syndrome more frequently and need more ventilation aid compared to those with normal myocardium. It must be kept in mind that almost all available COVID-19 investigations have ignored subclinical patients, which might skew the percentages and cut-off limits substantially and deteriorate our understanding about the true behavior of SARS-CoV-2. However, it seems that there is no way!

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Authors' Contribution

Study concept and design: I.R., M.Z. and Z.E Analysis and interpretation of data: Z.E. and Z.D. Critical revision of the manuscript for important intellectual content: I.R., Z.E., Z.D., and M.Z.

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