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Cardiovascular Considerations in COVID-19: A Brief Overview

Kudrat Singh[1], Anahat Puar[2], Amreen Dhindsa[3]
[1,2,3]Paras Hospitals, Panchkula, India

ABSTRACT: The spread of coronavirus disease (COVID-19) led to a world-shattering pandemic which impacted humanity in a severe manner. Research suggests that coronavirus has multiorgan effects. It has brought together researchers of all fields who are trying to understand the pathophysiology of the disease and define most select treatment strategies. Pre-existing comorbidities such as hypertension, cardiovascular disease (CVD) and diabetes are linked with a higher mortality rate of COVID-19. With its widespread effects and different strains, there is escalating apprehension about the cardiovascular effects of the viral infection, like myocarditis, thrombosis and arrhythmias, and its relation with existing CVD and heart related problems. The cardiovascular manifestations of COVID-19 need to be understood well for cardiologists and other health workers to be able to diagnose and treat them in the upcoming time.

KEYWORDS: Arrhythmia; Cardiovascular; COVID-19; Myocarditis; Thrombosis

I. INTRODUCTION

Severe acute respiratory syndrome corona virus 2 (SARS-CoV2) which causes COVID-19 was first reported in Wuhan, China on 31st December, 2019 and has profoundly impacted all fields of medicine since then [1]. Even though the epicentre for the disease was China, by March 2020, the number of cases outside China surpassed the number of those within. It rapidly malformed into a global pandemic and within a month after that, by April 2020, over 1.8 million cases and 110000 deaths were reported worldwide, upsetting 185 countries [2]. The early presentations from Wuhan were consistent with viral pneumonia and consequent deep sequencing confirmed a novel RNA- based virus of the Coronaviridae family [3]. The most common symptoms of COVID 19 consist of fever, dry cough, myalgia or fatigue, as is the case in other viral infections. Since the primary presentation of COVID-19, much has been learned about its pathophysiology and specific cardiovascular manifestations (see Figure 1). Studies suggest that patients with pre-existing cardiovascular conditions have higher rates of mortality to the COVID 19 disease. The disease also has numerous unique cardiovascular manifestations that include myocarditis, heart failure, a proclivity for thrombosis and arrhythmia [4]. Particular experimental therapies for COVID-19 infection have potential cardiovascular side effects as well. This review will sum up our understandings of the connection of CVD with COVID-19.Cardiovascular considerations regarding treatment strategies will also be discussed.

II. CARDIOVASCULAR COMORBIDITIES AS PREDICTORS OF FATAL OUTCOMES IN COVID-19

The prevalence of pre-existing CVD has been known to worsen infection in patients testing positive for COVID-19. The cardiovascular manifestations caused by this virus have also raised sizeable concern. Several studies have suggested findings as to which CVD increase the risk of a fatal

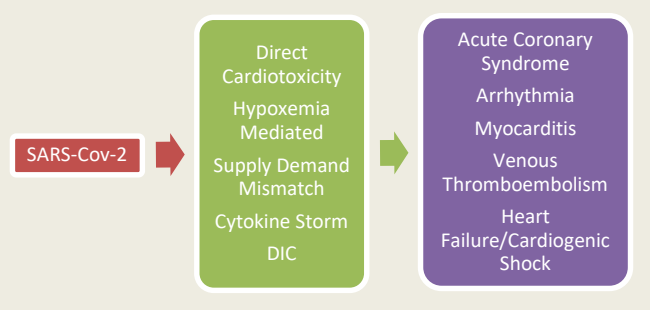

Figure 1: Mechanisms of cardiovascular injury due to COVID- 19. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; DIC, disseminated Intravascular Coagulation.

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Outcome post or during the viral infection. One such study with a sample of a small Chinese cohort revealed that patients with coronary artery disease were less likely to recover from their infection [5], while others displayed an association between heart failure [6], myocardial injury and increased risk. Another study that compared 138 patients who required admission to the intensive care unit to those who did not revealed that those admitted were more likely to have underlying comorbidities such as hypertension (58.3% vs 21.6%) in patients who were not admitted to the ICU, diabetes (22.2% vs 5.9%), CVD (25.0% vs 10.8%) and cerebrovascular disease (16.7% vs 1%) [4]. some studies have also revealed cardiovascular manifestations of the virus in patients with no pre-existing comorbidities. A study by Huang et al [1] reported acute myocardial injury in 12% of COVID-19 patients, which were mainly caused by elevated troponin T (TnT) levels. A study with a sample of 187 COVID-19 patients displayed that 66 (35.3%) patients had pre-existing CVDs such as hypertension, coronary heart disease and cardiomyopathy, while 52 (27.8%) patients presented with myocardial injury characterized by elevated TnT levels. The elevated TnT levels were more common in patients with pre-existing CVD. The mortality rate was 13.33% for patients with pre-existing CVD with normal TnT levels, 37.50% for those who did not have CVD but displayed elevated TnT levels, and 69.44% for patients with underlying CVD with elevated TnT levels. Patients with elevated levels of TnT also exhibited more malignant arrhythmias, use of glucocorticoid therapy (71.2% vs 51.1%) and mechanical ventilation (59.6% vs 10.4%). The findings revealed that there is an association between myocardial injury, characterized by cardiac dysfunction and arrhythmias, and a fatal outcome of COVID-19 [7].

III. SPECIFIC CARDIOVASCULAR COMPLICATIONS OF COVID-19

A. Myocarditis

Myocarditis can be defined as acute injury leading to myocyte damage, which results in activation of the innate and humoral immune system. This activation leads to severe inflammation that, if persists, leads to ongoing myocyte damage, symptomatic heart failure or death. It is essentially inflammation of the heart muscle. Myocarditis is a rare and potentially fatal condition and has various causes including viral, bacterial and protozoal infections, drug reactions, autoimmune diseases, giant cell myocarditis and sarcoidosis. It has also been seen as a manifestation of SARS-CoV2 in some patients [8] . One such case was observed in a 63-year-old male, admitted to the hospital with pneumonia and cardiac symptoms after visiting Hubei Province, China. After testing positive for COVID-19, he was also observed to have elevated levels of cardiac biomarker, troponin I (up to 11.37 g/L), diffuse myocardial dyskinesia and a reduced left ventricular ejection fraction (LVEF) on his echocardiography. The diagnostic criteria according to the Chinese expert consensus statement suggested fulminant myocarditis. Post diagnosis, the patient received antiviral therapy and mechanical life support, which reduced troponin I and interleukin-6 levels. LVEF was also observed to gradually increase. However, the patient died on the 33rd day in the hospital because of a worsening secondary infection [9].

Another study conducted by Sawalha et al found 14 cases with myocarditis post COVID-19 infection. The results suggested male predominance (58%) and a median age of 50.4 years. Most patients did not have pre-existing conditions, however the most common for those who did was hypertension (33%). Out of 11 cases that had documented hemodynamic status, a majority were in shock (cardiogenic and mixed cardiogenic and septic shock). Troponin levels were high in 91% of the cases [10] .

B. Acute Decompensated Heart Failure

Research suggests that COVID-19 is associated with an increased rate of hospitalization of patients for heart failure. Two case series from China adds to the association between COVID-19 and heart failure. In a sample of 113 and 191 patients, heart failure was seen in 49% and 52% deaths respectively. There seems to be a broad spectrum of severity of disease which affect cardiac manifestations and the type of treatment or support required. Fulminant heart failure requires inotropes, hypoxia or refractory shock requires mechanical circulatory support and ECMO is being used for Covid-19 cases [11,12] .

Although existing data suggests that cases of heart failure would have increased due to Covid-19, some data suggests that hospitalization for heart failure has declined during the pandemic, but an increase in mortality in the hospitals has been observed. Various reasons have been suggested for this, such as a fear of hospitals due to the virus which could have led to a decrease in hospital visits. However, more research is required to study the reasons for increased in-hospital mortality [13].

C. Acute Coronary Syndromes

Acute coronary syndromes are a range of different conditions that cause reduced blood flow to the heart. One such condition is myocardial infarction, often referred to as a heart attack in which cell death leads to damaged or destroyed heart tissue. Association

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with acute coronary syndrome has been observed in infections similar to COVID-19, such as influenza, respiratory syncytial virus and bacterial pneumonia. It is hence hypothesized that COVID-19 would also cause an increase in acute coronary syndromes.

Myocardial injury with ST-segment elevation has also been seen in COVID-19 patients. A study based on 6 New York hospitals with patients experiencing ST-segment elevation revealed that the presentation of this was extremely variable with a high prevalence of nonobstructive disease and poor prognosis [14]. Previous studies revealed that 64% of the patients with ST-segment elevation related myocardial infarction had normal D-dimer levels, while this study found all 18 patients to have elevated D-dimer levels. Myocardial injury is therefore complex and could be due to plaque rupture, hypoxia, coronary spasm, cytokine storm and other diseases.

Although coronary syndromes and myocardial infarctions are likely to increase during the pandemic, some studies show otherwise. There has been a significant reduction in admission to the hospital for acute ST-segment elevation myocardial infarction (STEMI) in a 1 week period in 2020 (once the pandemic began) as compared to the previous year. There was a 48.4% reduction, with a 26.5% reduction for STEMI admissions and a 65.4% reduction for non-ST segment elevation myocardial infarction (NSTEMI). There was also greater decrease for women (41.2%) as compared to men (25.4%). The fatality rate of STEMI also increased from 4.1% to 13.7% in 2019, with an increase in rate of complications such as cardiogenic shock, arrhythmias, cardiac rupture etc from 10.4% to 18.8%. It is clear from the increase in fatality rate that COVID-19 patients have been affected by complications like acute coronary syndromes and the decline in admission rates has been hypothesized to exist for other reasons. Some suggest that people are staying at home due to a fear of hospitals and are attempting to treat themselves until lockdown restrictions are less strict, while others suggest that social distancing could be causing low exertion which could cause cardiac symptoms [15]. It is also possible that people are so fearful of the hospital that they are ignoring symptoms of cardiac issues completely in an attempt to avoid exposure to infection at the hospital. This could explain increase in rate of heart failure due to late presentation of heart attacks or heart disease.

D. Thrombosis

Thrombosis is a condition which occurs when blood vessels are blocked by blood clots. Pulmonary embolism (PE) can be described as a blood clot (thrombus) getting stuck in an artery in the lung, which results in blockage of blood flow to that part of the lung. Deep vein thrombosis (DVT), on the other hand, occurs when a blood clot develops in one or more deep veins in the body, most commonly in the legs. Both these thrombotic events have been commonly observed in patients with severe COVID-19 infection. Initial reports show occurrence of 20%-30%. A Dutch study with 184 COVID-19 patients in the intensive care unit (ICU) revealed that 49% of the patients had large-vessel thrombotic events, observed to be majorly pulmonary emboli in the segmental and subsegmental pulmonary arteries. Patients experiencing such thrombotic events were also at a higher risk of all-cause death (5-fold higher) as compared to patients who did not display signs of thrombosis [16]. Another study of an Italian sample of 388 COVID-19 patients also displayed a 21% rate of incidence of thromboembolic events. Half of these events were diagnosed in the first 24 hours the patients spent at the hospital [17]. The high occurrence of thrombotic events calls a need to study the true prevalence of thrombosis in COVID-19 patients, with the stage of the disease and the ward in which the patient is diagnosed being important considerations. For example, a patient in the intensive care unit with thrombosis would imply that the patient was severely ill with the viral infection and this would be helpful to determine at which stage thrombosis occurs. Some studies have compared the rates of thrombosis in patients in the ICU versus those in the general ward. One such study revealed that the occurrence was 10% at 2 weeks in ward patients versus 48% in ICU patients. Another study found the incidence to be 18% in non-ICU patients and 50% in ICU patients [18]. These results have also triggered a search for the best treatment and its efficacy. To determine this, 99 patients from a study of 449 patients with COVID-19 were given mainly low molecular weight heparin for 7 days or more. This anticoagulant therapy was found to be associated with a better outlook in severe COVID-19 patients [19]. More research is thus required for treatment therapies and the one best suited for the high incidence of thrombosis as a post-complication of COVID-19.

E. Arrhythmias

With the current understanding of the coronavirus, cardiac arrhythmias have emerged as a common complication in severely affected Covid-19 patients. Possible reasons for this include hypoxia caused by direct viral tissue involvement of lungs, myocarditis, myocardial ischemia, myocardial strain, abnormal host immune response and other mechanisms [20]. A study based in the Seventh Hospital of Wuhan City, China evaluated 187 COVID-19 patients and their cardiac manifestations. Out of these patients, 27.8%

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had myocardial injury, which was followed by heart dysfunction or arrhythmias. During their admission to the hospital, it was found that patients with elevated TnT levels displayed more frequent malignant arrhythmias as compared to those with normal TnT levels. Other data suggests that 16.7% of 138 hospitalized COVID-19 patients were affected by arrhythmias. Myocardial injury was also found to be associated with cardiac dysfunction and ventricular tachyarrhythmias [21]. Data also suggested that rate of incidence of arrhythmia was higher in patients admitted to the intensive care unit (44.4% versus 6.0%; P<.001), with hypoxemia caused by the virus most commonly resulting in arrhythmia among elderly patients [22].

Another study that aimed to find the association between atrial arrhythmias and COVID-19 studied 115 COVID-19 patients at the University of Alabama at Birmingham Hospital. Of these 115 patients, 69 were admitted to the intensive care unit (ICU), while the remaining 46 were admitted to the general ward. Some had underlying comorbidities including 70% presenting with hypertension, 42% with tobacco use, 39% with diabetes, 16% with coronary heart disease, 14% with chronic kidney disease and 13% with chronic obstructive lung disease. Out of these 115 patients, 19 (16.5%) patients presented with atrial tachyarrhythmia, including atrial fibrillation in 12, atrial flutter in 6 and atrial tachycardia in 1 patient, all of which was not present when the patients were hospitalized. All of these patients were from the ICU and no patients admitted to the general ward developed atrial arrhythmia (p=0.00002). Analysis of these patients revealed that they were older than patients who did not experience arrhythmias and also had higher concentrations of C-reactive protein (CRP) and D-dimer but comparable levels troponin and brain natriuretic peptide (BNP). No difference in incidence of arrhythmia was observed in patients who were given remdesivir, hydroxychloroquine or azithromycin but the need for mechanical ventilation was strongly associated with atrial arrhythmias (p=0.0002) [23]. Although incidence of arrhythmias is slowly becoming more widely known, more research is required to highlight the trends in which this follows and the possible effect of SARS-CoV2 on the heart.

IV. CONSIDERATIONS OF TREATMENT THERAPIES OF CARDIAC MANIFESTATIONS OF COVID-19

Currently, there is no treatment available for COVID-19, but some therapies are being investigated regarding their efficacy to help patients testing positive for this virus. Some of these therapies include anticoagulant therapy, ACE inhibitors and angiotensin receptor blockers, immunosuppressive therapy, hydroxychloroquine and azithromycin, mechanical and cardiopulmonary support.

Anticoagulant therapy consists of medicines that help prevent blood clots. This is beneficial for COVID-19 patients due to the known manifestations of the virus such as thrombosis, which results in blood clot formation. To study its efficacy, a study of 449 severely affected COVID-19 patients was conducted. Anticoagulant therapy with mainly low molecular weight heparin was found to lower the mortality rate of patients meeting sepsis-induced coagulopathy criteria or those who had significantly high levels of d-dimer [24]. This therapy has shown some success, although more research is required. ACE inhibitors and angiotensin receptor blockers work have been identified as potential therapies after in-depth studies identifying the receptor at which SARS-CoV2 binds. Some studies have revealed that these inhibitors and receptor blockers prevent lung fibrosis and limit pulmonary disease progression making them protective in nature. However, there is a lot of controversy as to whether these inhibitors are effective or not [25]. Immunosuppressive therapy has been considered as a therapy on the basis of the serious effects of cytokine release syndrome associated with COVID-19 on cardiac pulmonary system. This therapy could help reduce the hyperinflammatory response of the virus [26]. Hydroxychloroquine and azithromycin are also potential treatment therapies. Chloroquine is a bioactive agent which has antiviral activity against DNA and RNA viruses [27]. Similar to chloroquine, hydroxychloroquine also has an effect on activated immune cells to decrease IL-6 expression [28]. On the other hand, azithromycin is a macrolide antibiotic that acts against Ebola viruses and others to suppress inflammatory processes [29]. Both these therapies seem beneficial and safe to use, however there has been some controversy regarding their cardiac side effects including prolongation of QT interval [30]. Lastly, mechanical and cardiopulmonary support are being used including intra-aortic balloon pump or veno-arterial ECMO on the basis of variable survival rates in respiratory failure in the past [31].

Various clinical trials are being conducted currently to find the most effective treatment therapy for different manifestations of SARS-CoV2 to lower the mortality rates and get a clearer picture of the way the virus works and ways to treat patients once infected.

V. CONCLUSION

The ongoing COVID-19 pandemic has posed a brutal threat to human life. Considering the numerous cases and their fatality, we have come to a conclusion that various cardiovascular co morbidities significantly impact severity of the disease. We saw excess

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mortality that far exceeded earlier coronavirus-related outbreaks. It has been seen that the elevated TnT levels which result to the severity of the disease were more common in patients with pre-existing CVD. Myocarditis has also been seen as a manifestation of SARS-CoV2 in some patients. Myocarditis has been found to be a relatively rare condition as compared to decompensation of pre-existing heart failure as a result of COVID-19. Thrombosis is another condition which occurs when blood vessels are blocked by blood clots. This has also been seen as another manifestation along with Acute Coronary Syndrome. It is clear from the increase in fatality rate that COVID-19 patients have been affected by such complications and the decline in admission rates has been hypothesized to exist for other reasons as well. Currently, there is no treatment available for COVID-19, but some therapies are being investigated regarding their efficacy to help patients testing positive for this virus.

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