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Review Article

Cardiovascular Manifestations of SARS CoV-2: A Review

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A B S T R A C T

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is a public health emergency of global concern. Besides the profound severe pulmonary damage, SARS-CoV-2 infection also causes a series of cardiovascular abnormalities, including myocardial injury, myocarditis and pericarditis, arrhythmia and cardiac arrest, cardiomyopathy, heart failure, cardiogenic shock, and coagulation abnormalities. COVID-19 patients with preexisting cardiovascular diseases are often at a much higher risk of increased morbidity and mortality. Number of mechanisms have been postulated for SARS CoV-2-associated cardiovascular damage including direct myocardial injury, systemic inflammation, hypoxemia, coronary thrombosis and drug-induced cardiac damage. Special attention should be given towards patients of SARS CoV-2 with concurrent cardiovascular diseases. Knowledge of the injury caused by SARS CoV-2 to the cardiovascular system and the mechanisms behind it is of the utmost importance to reduce the morbidity and mortality of these patients by treating them in time.

Keywords: SARS CoV-2, COVID 19, Cardiovascular Manifestation, Myocardial Injury, Myocarditis, Arrhythmia

Introduction

An outbreak of pneumonia of unknown cause was detected in Wuhan, Hubei province in December 2019.[1] These pneumonia patients underwent testing and gene sequencing leading to identification of the pathogen named as 2019 novel coronavirus (2019-nCoV), which was further named officially as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organisation (WHO).[2] SARS-CoV-2 has spread rapidly across China and became pandemic.[1] Symptomatic patients usually presented with fever, dry cough, shortness of breath, myalgia or fatigue. The median incubation period in COVID-19 is 5.1 days with majority of them (97.5%) becoming symptomatic within 11.5 days of infection.[2] In the current scenario, the statistics of SARS-CoV-2 are staggering and relentlessly mounting. It is very clear that the number of infections and deaths are continuously increasing with increasing need for critical care interventions. The clinical spectrum of SARS-CoV-2 ranges from mild to severe with a majority of them (81%) having mild symptoms while severe symptoms (defined as respiratory rate ≥30/min, hypoxia: blood oxygen saturation ≤90%, PaO2/FiO2 <300, and/or pulmonary infiltrates >50% within 24 to 48h) occur in 14% cases. Critical illness (defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure) have been reported in only 5% of subjects with overall Case Fatality Rate (CFR) of

2.3%.[3] studies have suggested that older population and persons with chronic health problems like Cardiovascular Disease (CVD) are at higher risk for COVID related morbidity and morbidity than the average population.[4,5] However, severe disease requiring hospital admissions and even expiries have been observed in younger individuals as well. Awareness about natural history of COVID-19 is increasing day by day but data regarding cardiovascular involvement are scarce. Usually respiratory symptoms dominate as clinical manifestations of COVID-19, but some of the cases have severe cardiovascular damage as well.[6] In addition, the presence of cardiovascular co-morbidities such as hypertension, coronary artery disease in these patients are often associated with poor prognosis.[3] So, knowledge of the injury caused by SARS-CoV-2 to the cardiovascular system and the mechanisms behind this is of utmost importance to reduce the mortality by treating these conditions in time.

Pathophysiology of Cardiac Manifestations

The mechanisms of cardiovascular damage from SARS-CoV-2 have not been fully understood however, it seems to be due to multiple factors. The common pathological mechanisms involved in causing cardiovascular complications are: direct myocardial injury, systemic inflammation, hypoxia induced injury and rupture of plaque and coronary thrombosis.

Direct Myocardial Injury

Angiotensin-Converting Enzyme 2 (ACE2) is a membrane-bound aminopeptidase that plays an important role in cardiovascular and immune systems.[7] ACE2 has a major role in cardiac functioning and the development of high blood pressure and diabetes mellitus. ACE2 has been found as a functional receptor for SARS-CoV and SARS-CoV-2.[7] SARS-CoV-2 infection is caused following binding of viral spike protein to human Angiotensin-Converting Enzyme 2 (ACE2) receptor which is expressed in the lungs (on type II pneumocytes), oral mucosa, heart, intestine, kidneys and vascular endothelium. Organ distribution of ACE2 seems to be closely related to the clinical involvement. The binding of SARS-CoV-2 to ACE 2 results in alteration in ACE2 signaling pathways that leads to acute myocardial injury as well as lung injury. Binding of SARS-CoV-2 to ACE2 prevents the enzyme from converting Ang II to Ang 1–7, potentiating Ang II-induced biological effects including pro-inflammation, pro-fibrosis, pro-oxidation, and vasoconstriction leading to cardiovascular and lung injury in the face of SARS-CoV-2 infection.[8,9] Ang 1-7 offers an array of benefits including ant inflammation, anti-fibrosis, anti-oxidation, and vasodilatation.[8]

Systemic Inflammation

Severe form of infection with SARS-CoV-2 is characterized by acute systemic inflammatory response and cytokine storm which results in immune mediated injury to various organs leading to multiorgan dysfunction. Cytokine storm syndrome denotes a severe life-threatening condition manifested by overwhelming inflammation, a sharp rise in proinflammatory cytokines, acute phase reactants like IL-6, hyperferritinemia, CRP, hemodynamic instability, and multi-organ failure, and is potentially fatal if untreated.[10] The hallmark of cytokine storm is an uncontrolled and dysregulated immune response involving continued activation of lymphocytes, macrophages, and natural killer cells.[11] The viral RNA serves as the main pathogenic molecule which binds to the pattern recognition receptors such as Toll-Like Receptor (TLR) 3, TLR7, TLR8 and TLR9. This leads to triggering of the downstream inflammatory cascade and activation of nuclear factor-κB (NF-κB) and Interferon Regulatory Factor 3 (IRF3) commencing in production of IFN-α /β and other pro-inflammatory molecules such as IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, GCSF, IFN-γ and TNF-α amongst which IL-6 is the most important one. This massive production of cytokines leads to increased vascular permeability, alveolar epithelial damage, ARDS followed by multisystem involvement.[12] The syndrome mainly impairs the cardiovascular system and manifests as severe heart failure and cardiogenic shock, accompanied with extracardiovascular symptoms including fever, lymphadenitis, rashes on hands and feet, and stomach ache.[13]

Hypoxemia

There is already a state of increased cardiometabolic demand in heart due to systemic inflammation. Hypoxia further alters myocardial demand-supply ratio causing acute myocardial injury, arrhythmia and shock. In addition, influx of calcium ions can be induced by hypoxemia and cause apoptosis and injury to cardiomyocytes.[14]

Coronary Thrombosis and Plaque Rupture

Coronary artery disease of Img duration along with the risk factors of atherosclerotic disease may enhance the occurrence of acute coronary syndrome after an infection as already shown in epidemiologic and clinical studies of influenza virus and other acute inflammatory conditions.[15-17] Infection triggers an increase in myocardial oxygen demand, which precipitates myocardial injury and infarction. Hypoxia too has been postulated as one of the causes of hypercoagulable states in these patients. In the same sequence, circulating cytokines released at the time of severe systemic inflammatory response may cause the breaking of atherosclerotic plaque and its instability. Pro-inflammatory cytokines may itself lead to endothelial injury and activation of coagulation cascade.[18] In such scenario, levels of D-dimer which serves as marker of fibrinolytic activity is elevated along with other inflammatory cytokines. Individuals with cardiac disorders are also at risk for hemodynamic decompensation at the time of stress due

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to severe infectious illnesses. Critically ill patients with COVID-19 are at an increased risk for venous thrombosis and hence the need for anticoagulation in these patients is justified.

Drug-Induced Cardiovascular Toxicity

At this point, antiviral drug-induced cardiovascular toxicity in SARS-CoV-2 treatment should not be ignored. Antiviral drugs including IFN-α, ribavirin, chloroquine phosphate, lopinavir/ritonavir and remdesivir have all been included in the treatment of COVID-19.[19] Several antiviral drugs exert cardiotoxicity or elicit interactions with other cardiac medications. For instance, lopinavir/ ritonavir may lead to prolongation of PR and QT intervals and influence serum levels of antiplatelet drugs through CYP3A4 inhibition.[20] Hydroxychloroquine (HCQ) mainly acts by (a) inhibiting ACE2-mediated viral entry hence preventing SARS CoV- 2 infection and (b) anti-inflammatory and immunomodulatory property hence attenuating the cytokine storm. However, due to its inherent property of blocking the hERG/Kv11.1 potassium channel, it can prolong the QT interval and increase risk of Torsades de pointes (TdP) especially in patients with congenital long QT syndrome.[20] This risk further gets compounded when drugs like azithromycin or lopinavir and ritonavir are prescribed simultaneously with HCQs.

Other Possible Mechanisms

Any systemic illness when critical can cause electrolyte imbalances which can precipitate arrhythmias especially in patients with preexisting cardiac disorders. Hypokalemia, in particular, resulting from the interaction of SARS-CoV-2 with renin angiotensin system (RAS) increases the vulnerability of heart to various tachyarrhythmias.

COVID-19 and Cardiovascular Manifestations

Studies available so far depicts close relationship between cardiovascular disease and SARS or MERS.[4] Patients of SARS-CoV infection experiences a variety of cardiovascular complications like tachycardia (71.9%), hypotension (50.4%), bradycardia (14.9%), reversible cardiomegaly (10.7%) and transient atrial fibrillation.[8] Elevation of cardiac biomarkers, arterial and Venous Thromboembolism (VTE), cardiogenic shock and arrest are the other cardiovascular manifestations of COVID-19. An observational study on Covid-19 patients has shown complications like shock (8.7%), acute cardiac injury (7.2%), arrhythmias (16.7%), acute respiratory distress syndrome (ARDS) (19.6%), and acute kidney injury (3.6%).[21] Particular forms of cardiovascular complications or aggravation of preexisting cardiovascular conditions in COVID-19 patients are discussed in detail here.

Acute Myocardial Injury

Myocardial injury, characterized by elevated levels of cardiac biomarkers, results from myocardial ischemia and non-ischemic causes including myocarditis.[22] Several studies have noted acute myocardial injury in patients with SARS CoV-2 which mainly manifested as follows: (1) cardiac biomarkers (hypersensitive cardiac troponin I) > 99th percentile upper reference limit; or (2) new abnormalities on electrocardiogram or echocardiogram.[23] In a series of 41 patients from Wuhan, China evidence of myocardial injury was seen in 12% (5) with majority of them 4 (80%) requiring ICU care.[24] Similarly, Wang *et al.* documented evidence of acute cardiac injury in 7.2% (10/138) patients of SARS CoV-2, of whom 8 (80%) required an ICU care.[25] A higher utilization of ICU care among these patients with myocardial injury suggests a more severe and advanced disease process in them. In a meta-analysis of 341 patients from China (four studies), it was seen that cardiac troponin I levels were significantly higher in patients with severe disease (standardized mean difference 25.6 ng/l; 95% CI [6.8-44.5]). The authors postulated that an early measurement of cardiac troponins immediately post admission would help identify a subset of patients with cardiac injury thus portraying a worse outcome.[26]

The mechanism for myocardial injury include virus mediated direct myocardial injury, immune mediated myocardial injury (systemic inflammation) and hypoxemia, as elaborated in pathophysiology.[27] An autopsy-based case report documented few mononuclear inflammatory infiltrates in myocardial interstitium on cardiac biopsy in a patient who succumbed to SARS- CoV-2.[28] Another report has documented the presence of low grade myocardial inflammation and viral particles in the myocardium (electron microscopy) on endomyocardial biopsy in a patient of SARS CoV-2 with cardiogenic shock.[29] Cytokine release syndrome or cytokine storm, a weakly known immunopathological condition due to hyperinduction of proinflammatory cytokines like interleukin (IL)-1, IL-6, T helper 1 cytokine interferon-gamma, and Tumour Necrosis Factor-alpha (TNF-α), has been found in the mechanism of SARS, MERS, and influenza.[30,31] In a retrospective series of 54 patients of SARS CoV-2, CRP levels were higher in patients with myocardial injury than those without indicating a severe inflammatory response in the former group.[32] Thirdly, hypoxemia as a part of respiratory failure in these patients may lead to myocardial oxygen demand supply mismatch especially in those with preexisting cardiac disease culminating in myocardial damage.

Two articles from two different academic hospitals in Wuhan, China, which was the epicenter of SARS CoV-2 favored the concept that inflammation is a potential mechanism for myocardial injury.[25,33] *Shi et al* did a cohort study on 416 admitted cases with COVID-19 positivity by RT-PCR out of which 82 (19.7%) had elevated high-sensitivity troponin I (TnI) levels, indicating myocardial injury with a

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higher mortality rate of 51.2% (42/82).[34] Similar results were reported by *Guo et al* in 187 admitted patients of SARS CoV-2, of whom 27.8% (52) had increased levels of troponin T (TnT), and mortality of 59.6% (31/52).[35] They reported that even if the functional and morphological cardiac dysfunctions were infrequent with elevated troponin values, it had a significant hazard ratio of 8.9 (95% confidence interval 1.9-40.6) for the risk of expiry, as reported by others.[25] *Guo et al* reported that TnT values are significantly linked with C-reactive protein and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values thus associating myocardial injury to the grade of inflammation and ventricular dysfunction. They also showed that progressive serial increase in both TnT and NT-proBNP values are associated with worse outcome.[35]

Acute Coronary Syndrome (ACS)

As with other infectious diseases, including SARS and influenza, COVID-19 can trigger ACS.[36,37] In early studies from China, a small proportion of patients with COVID-19 presented with chest pain on admission to hospital, but the characteristics of the chest pain were not described.[4] In a case series from New York involving 18 patients with SARS CoV-2, and ST segment elevation indicative of potential acute myocardial infarction, five of the six patients with myocardial infarction required percutaneous coronary intervention.[38] In a case series from Italy involving 28 patients of SARS CoV-2 and ST segment elevation myocardial infarction (STEMI), myocardial infarction was the first clinical manifestation of SARS CoV-2 in 24 patients and clinical assessment by coronary angiography showed that 17 patients had evidence of a culprit lesion that required revascularization.[39] This suggests that SARS CoV-2 can cause ACS even in the absence of substantial systemic inflammation. However, the incidence of ACS in patients with SARS CoV-2 is still unknown. Considering the overwhelmed health-care facilities of many cities during the COVID-19 outbreak, the number of cases of acute myocardial infarction among patients with COVID-19 might be an underestimation in early studies. The underlying mechanism for SARS CoV-2 induced ACS might involve plaque rupture, coronary spasm or microthrombi in coronary vessels owing to systemic inflammation or cytokine storm.[40] Activated macrophages secrete collagenases that degrade collagen, a major constituent of the fibrous cap on atherosclerotic plaques, which can lead to plaque rupture. Activated macrophages are also known to secrete tissue factor, a potent procoagulant that triggers thrombus formation when the plaque ruptures.[40] SARS CoV-2 induced direct endothelial or vascular injury might also increase the risk of thrombus formation and subsequent ACS.[41] Despite the potential for SARS CoV-2 to induce ACS, the number of reported cases of ACS during the outbreak in Italy, Spain and the USA was actually significantly lower than during pre-COVID-19 periods, with a reported 42-48% reduction in hospitalizations for ACS and a 38–40% reduction in percutaneous coronary interventions for STEMI.[42] In contrast, the incidence of out-of-hospital cardiac arrest increased during this period, which was strongly associated with the cumulative incidence of COVID-19.[43] This decline in number of patients with myocardial infarction seeking urgent hospital care during the peak of the outbreak was also reported in an extensive global survey by the ESC.[43]

Myocarditis and Pericarditis

Myocarditis can be one of the clinical presentations of SARS CoV-2 infection, however, its exact pathogenesis is still not clear. Viral infections like influenza and parvovirus B-19 are common causes of myocarditis.[30,25] Viral myocarditis may present as either as focal or global myocardial inflammation, necrosis, and ventricular dysfunction. The data on the incidence of fulminant myocarditis in SARS CoV-2 is very much limited. Zeng *et al*. reported the first case of SARS CoV-2 presenting with fulminant myocarditis in a 63-year-old male with no underlying cardiac disease.[44] On admission, cardiac enzymes (troponin-I: 11.37 g/l, myoglobin: 390.97 ng/ml) and N-terminal brain natriuretic peptide (NT BNP: 22600 pg/ml) were elevated. ECG showed sinus tachycardia with no ST elevation. Echocardiography revealed enlarged cardiac chambers, dyskinetic myocardium with decreased LVEF (32%). Similarly, Hu and colleagues reported a 37-year-old SARS CoV-2 positive male who presented with acute onset chest pain and hypotension with ST elevation in inferior leads and raised cardiac enzymes and BNP.[45] CT coronary angiography revealed normal epicardial coronaries while echocardiography showed enlarged cardiac chambers, severely decreased ventricular function (LVEF: 27%) with minimal pericardial effusion. He tested negative for other viruses causing myocarditis. Patient improved markedly with IV corticosteroids, immunoglobulins and inotropic support along with broad spectrum antibiotics (pre-discharge LVEF: 66%). Most of the diagnoses of myocarditis have been made based on clinical and ECG findings, elevated cardiac enzymes, echocardiographic evidence with normal coronaries on coronary angiogram.[46] In an analysis of 68 fatal cases of SARS CoV-2, 5 patients (7%) were found with fatal fulminant myocarditis in combination with circulatory failure, and 22 fatalities (33%) were attributed to both myocarditis and respiratory failure.[47] Direct localization of SARS CoV- 2 in myocardium and systemic inflammatory response may attribute to myocarditis in these patients .

Arrhythmia and Cardiac Arrest

Cardiac arrhythmias both tachy- as well as brady-arrhythmias are common in patients with SARS CoV-2. Wang *et al*. reported 16.7% (23/138) prevalence of cardiac arrhythmias in SARS CoV-2 out of which 16 (44.4%) required ICU care. However, details of these arrhythmias were not mentioned.[25] Hui and colleagues reported ECG findings in 17 patients, of whom only three had tachycardia in severe and

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critical cases.[48] Atrial fibrillation was reported in two patients with critical illness both of whom had a fatal outcome. Guo *et al*. reported ventricular tachycardia/ventricular fibrillation in 5.9% (11/187) patients with SARS-CoV-2 infection.[35] Patients with elevated cardiac troponins had a significantly higher frequency of malignant arrhythmias compared to those without (9 *vs* 2; p<0.001) it. This highlighted the fact that patients with myocardial injury had far greater prevalence of tachyarrhythmias. This high frequency of arrhythmias may in part be due to metabolic causes such as electrolyte disturbances, neurohormonal activation or hypoxia especially in those who are critically ill. Similar findings have been documented in previous SARS pandemic with tachycardia being most common finding seen in 2/3rd of patients.[49]

Venous Thromboembolism

Patients with COVID-19 disease are at a high risk of Venous Thromboembolism (VTE) especially those who are critically ill with prolonged immobilization. Apart from venous stasis due to prolonged immobilization, hypercoagulability due to use of steroids, immunoglobulins as well as vascular endothelial damage due to central venous catheterization and/or ECMO can often contribute to the occurrence of VTE. Hypoxia too has been postulated as one of the causes of hypercoagulable states in these patients. Although none of the studies have reported prevalence of VTE, few case reports have mentioned the occurrence of pulmonary embolism in these patients. Xie *et al* reported acute pulmonary embolism in two patients aged 57 and 70 years with elevated D-dimer and multiple filling defects on CT pulmonary angiogram.[50] Danzi *et al* reported a case of 75-year-old female with pulmonary embolism and right ventricular dysfunction on TTE.[51] Multiple studies from China have reported higher D-dimer levels in SARS CoV-2 patients with adverse outcomes. Zhou *et al.* reported elevated D-dimer levels which was strongly associated with greater in-hospital mortality (OR: 18.4; p=0.003).[52] Another study showed that D-dimer levels were significantly higher in non-survivors than survivors (2.12 µg/ml *vs* 0.61 µg/ml; p<0.001) thus reflecting a worse prognosis. Majority of the non-survivors met the criteria for DIC.[53] Multiple reasons can be postulated for activation of coagulation cascade in critically ill-patients which include i) pro-inflammatory cytokines leading to activation of coagulation cascade especially in critically ill patients and D-dimer is a marker of fibrinolytic activity; ii) during inflammatory conditions, the alveolar hemostatic balance is tilted more towards a prothrombotic state; iii) proinflammatory cytokines may lead to endothelial injury and activation of coagulation cascade.[54-56] Levels of D-dimer which serves as marker of fibrinolytic activity is elevated along with other inflammatory cytokines. Critically ill patients with SARS CoV-2 are at an increased risk for venous thrombosis and hence the need for anticoagulation in these patients. In the Chinese cohort of SARS CoV-2 patients, an early use of anticoagulation was initially recommended.[57] D dimer has a limited predictive value for venous thromboembolism especially in critically ill and hospitalized patients hence, VTE risk assessment should be done on an individualized basis. Another factor to be considered regarding anticoagulation is that most of the patients are elderly with multiple comorbid conditions hence an increased bleeding risk. A recent study showed that in COVID-19 positive patients with sepsis-induced coagulopathy score <4, administration of heparin led to reduced 28-day mortality. This showed that anticoagulant therapy had better outcomes in only selected group of patients.[58] Anticoagulation with heparin thus has been recommended by few experts in China based on the limited data.[59] Many authors suggested the use of Low Molecular Weight Heparin (LMWH) over Unfractionated Heparin (UFH) for the treatment of confirmed or suspected VTE whenever possible in patients with SARS CoV-2 infection. This approach avoids additional laboratory monitoring, minimizes nursing and phlebotomy exposure, and limits use of personal protective equipment. Due to lack of evidence on outcomes for bleeding or thrombosis, authors do not recommend dosing adjustments of LMWH using anti-Xa levels. They recommend use of UFH over LMWH in patients with acute kidney injury or in patients with creatinine clearance less than 15-30 ml/min. They recommend using an anti-Xa assay rather than an aPTT to monitor therapeutic UFH in patients with COVID-19 whose aPTT is prolonged at baseline. If the baseline aPTT is normal, it is reasonable to monitor therapeutic UFH with either an anti-Xa assay or aPTT. They also suggested the clinicians to consider reasons other than SARS CoV-2 for baseline aPTT prolongation, as this laboratory finding could be due to an underlying coagulopathy that increases the risk of anticoagulant associated bleeding.[60]

Cardiomyopathy and Heart Failure

Several studies have noted the occurrence of cardiomyopathy in patients with SARS CoV-2. Among 21 critically ill patients with SARS CoV-2, cardiomyopathy developed in 7 (33.3%) patients.[61] Meanwhile, in a single-centered observational study of 187 patients with confirmed SARS CoV-2 eight patients had preexisting cardiomyopathy although little follow up evaluation was performed on the outcome in these patients.[37,62] It is worth noting that a number of medications used in SARS CoV-2 may also lead to cardiomyopathy, including chloroquine, and interferon.[63] Heart failure is a common complication of SARS CoV-2 due to deterioration of preexisting cardiac function and newly developed cardiomyopathy and myocarditis. In a multi-centered cohort study involving 191 SARS CoV-2 patients, heart failure was noted in 23% of patients, and more prevalent in non-survivors compared to survivors (52% versus 12%,

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P < 0.0001).[64] Heart failure is characterized by decreased left ventricular ejection fraction and drastically elevated NT-proBNP. Guo and colleagues reported a higher level of cardiac biomarkers and NT-proBNP in patients with elevated troponin T.[33] Moreover, a tight correlation was identified between NT-proBNP and troponin T levels, indicating that patients with myocardial injury are at higher risks of cardiac dysfunction or heart failure.[33] Although patients of SARS CoV-2 patients often have comorbidities that can affect cardiac diastolic function like diabetes, hypertension and obesity, few studies so far have revealed a relationship between Heart Failure with preserved Ejection Fraction (HFpEF) and SARS CoV-2. Sinkey and colleagues reported that HFpEF developed in a postpartum patient with SARS CoV-2 and preeclampsia.[65] Notably, loss of Angiotensin-Converting Enzyme 2 (ACE2), the receptor for SARS CoV-2, increases the proinflammatory macrophage phenotype in the heart from patients with HFpEF.[66] More studies are warranted to explore the interplay between SARS CoV-2 and HFpEF. In SARS CoV-2 patients heart failure can be attributable to myocardial injury, systemic inflammatory response, ARDS and pulmonary hypertension, retention of water and sodium, renal dysfunction and imbalance between myocardial oxygen demand and supply.

Cardiogenic Shock

Although direct evidence for incidence rate of cardiogenic shock in patients infected with SARS CoV-2 is little, cardiogenic shock has been demonstrated as a severe complication of SARS CoV-2. In a 69-year-old patient with confirmed SARS CoV-2, elevated inflammatory markers and increased hypersensitive troponin I were noted prior to the development of severe cardiogenic shock.[67] Cardiogenic shock may be mixed with other types of shock, like septic shock in SARS CoV-2 infection. In a study involving 138 patients with SARS CoV-2, 8.7% of patients had confirmed shock but subtypes of the shock were not mentioned. Shock was seen more often in patients who were admitted to ICU than in the non- ICU patients (30.6% Vs 1.0%, P < 0.001).[68]

Management Related Cardiac Manifestation

As the COVID-19 pandemic has widened its grip, "off label" re-purposing of various drugs such as HCQ, azithromycin and lopinavir/ritonavir has been done in a bid to halt its march. However, with the usage of these drugs there has been the inadvertent risk of QT prolongation, TdP and sudden cardiac death. HCQ has shown promising results in in-vitro studies and is being increasingly used both for treatment as well as post-exposure chemoprophylaxis.[69] However, it can prolong the QT interval and increase risk of TdP especially in patients with congenital long QT syndrome. This risk further increases with concomitant use of drugs like azithromycin or lopinavir and ritonavir with HCQs. A baseline 12-lead electrocardiogram should be performed in all SARS CoV-2 positive patients planned to receive these drugs along with serial monitoring in those with prolonged QTc interval. In addition, renal and hepatic functions, serum electrolytes should also be measured. In patients with QTc values <99th percentile for age/gender (460 ms in pre-pubertal males/females, 470 ms in postpubertal males, and 480 ms in postpubertal females) there is a low risk of TdP and hence drugs such as HCQ/chloroquine, lopinavir ritonavir or azithromycin can be initiated without delay. In patients with QTc >500 ms, a search should be made to identify all correctable cause of prolonged QT (drugs, electrolytes) and a risk benefit analysis should be done prior to start of therapy. If these patients are started on such drugs, it is recommended to use HCQ alone rather than a combination with azithromycin and frequently monitor the QTc intervals. In patients with QTc values <99th percentile for age/gender prior to therapy and while on treatment, the QTc >500 ms or QTc increases by >60 ms, azithromycin should be discontinued and or dose of hydroxychloroquine be reduced followed by daily ECG monitoring. If despite this the QTc >500 ms, it is prudent to perform a risk-benefit analysis in order to discontinue HCQ.[58,69] In addition, chloroquine affects beta-receptor blockers through inhibition of CYP2D6.[70] Therefore, blood pressure and heart rate must be closely monitored when co-administration of β-blockers and chloroquine in SARS CoV-2 patients. Remdesivir, previously administrated to patients with Ebola viral infection, is now being used in COVID-19 patients. During Ebola outbreak, one patient (among a total of 175 patients) administered with loading dose of remdesivir developed severe hypotension and sudden cardiac arrest.[71]

COVID-19 with Underlying Cardiovascular Co-morbidities

Patients with pre-existing co-morbidities tend to be more vulnerable to SARS CoV-2 infection as well as its complications with poor clinical outcomes. A meta-analysis of 8 studies including 46,248 patients from China reported that most common comorbidities in this population group were hypertension (17±7%, 95% CI: 14-22%), diabetes (8±6%, 95% CI: 6-11%) and cardiovascular disease (CVD) (5±4%, 95% CI: 4-7%). The odds of hypertension (OR: 2.36, 95% CI: 1.46-3.83) and CVDs (OR: 3.42, 95% CI: 1.88-6.22) were higher in severe patients as compared to non-severe group.[72] In one of the largest series of SARS CoV-2 patients (n=44,672), comorbidities such as hypertension were reported in 12.8%, diabetes in 5.3% and CVD in 4.2% subjects. The case fatality rate (CFR) was higher among patients with co-morbidities such as CVD (10.5%), diabetes (7.3%) and hypertension (6%) as compared to those without (CFR:0.9).[3] another study among 1591 patients from Italy reported hypertension (49%), CVDs (21%) and hypercholesterolemia (18%) in SARS CoV-2 patients. Patients

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with hypertension were significantly older, required higher PEEP levels, had lower PaO2/FiO2 and higher ICU mortality.[73] data regarding mortality in COVID-19 released by National Health Commission of China showed that 35% of patients were hypertensive while 17% had prior history of CAD.[74] Similar findings were previously observed in SARS pandemic as well as MERS-CoV outbreak.[75,76] In SARS outbreak, co-morbidities such as diabetes and CVD were reported in 11% and 8% subjects respectively with an increased risk of mortality in these groups.[74] Similarly, in MERS-CoV outbreak, diabetes and hypertension were present in nearly half of the cases while CVD in nearly one-third of them.[77] The proposed hypothesis for increased severity of disease in patients with CVDs is that a majority of them are elderly with lower ACE2 levels and higher angiotensin signaling. As SARS-CoV-2 virus binds to ACE2, there occurs a decreased ACE2 expression and hence critically low ACE2 levels leading to higher angiotensin II levels. This leads to a more severe expression of disease in patients with co-morbidities.[78]

Long Term Impact of Covid-19 on Cardiovascular System

As we are still in the nascent stages of COVID-19 pandemic, data regarding the long-term impact on the cardiovascular system need to be evaluated. Sparse data exists regarding the long term impact of SARS CoV-2 infection on the cardiovascular system. Hospitalization for pneumonia increases both short term as well as long term CVD (myocardial infarction, stroke, and fatal coronary heart disease) risk. This has been attributed to the heightened systemic inflammatory and pro-coagulant activity seen in these patients.[79] It has been seen that survivors of SARS epidemic have suffered metabolic derangements over a long follow-up period. A study involving 25 SARS survivors showed that these patients had higher predisposition to develop hyperlipidemia (68%), CVA (44%) and abnormal glucose metabolism (60%) over a period of 12 years as compared to healthy volunteers. In addition, these patients had significantly higher lipid levels as compared to the controls which had been attributed to the high-dose pulses of methylprednisolone used during the acute illness.[80] however, in a 12-year longitudinal study to determine long-term outcomes in patients with SARS treated with oseltamivir, no significant difference in cardiac parameters was reported among the two groups.[81]

Many patients developing ARDS survive the acute phase of the illness but a substantial proportion may die as a result of progressive pulmonary fibrosis.[82] Importantly, an autopsy based study of 159 patients having ARDS, fibrosis was found to be in 4% of patients with disease duration of less than 1 week, (24%) of patients with disease duration between 1-3 weeks, and (61%) in patients with disease duration more than 3 weeks. This suggests that any potential antifibrotic treatment should be considered from the very first week of ARDS onset.[83] A substantial proportion of patients developing ARDS will have residual long-term impairment of lung function and radiological (CT) evidence of pulmonary fibrosis with anterior reticulation, which is the dominant abnormality seen in upto 85% of survivors.[82,84] Multiple aberrant host pathways interconnect resulting in pulmonary fibrosis in a subset of individuals developing ARDS. Dysregulated release of matrix metalloproteinases during the inflammatory phase of ARDS causes endothelial and epithelial injury, and unchecked fibro proliferation. In this regard, canonical profibrotic pathways regulated by TGF-β47 are very important and vascular dysfunction being a key component for switching from ARDS to fibrosis, with VEGF97 and cytokines like TNFα and IL-6 implicated in it.[82,85] It is not clear why certain individuals recover from such an insult whereas others show progressive pulmonary fibrosis. Data from previous coronavirus infections like SARS and MERS and upcoming data from current SARS CoV-2 pandemic suggests that substantial fibrotic consequences may there following SARS CoV-2 infection.

Chronic hypoxemia due to fibrosis and loss of lung parenchyma might contribute to the development of pulmonary hypertension and right ventricular hypertrophy by obliterating pulmonary vascular beds.[86] Chronic hypoxemia may lead to myocardial oxygen demand supply mismatch resulting into myocardial damage as well. Antifibrotic therapy available so far theoretically might have a role in preventing fibrosis developing after SARS-CoV-2 infection but their exact role is yet to be seen.

Conclusion

The ACE2 receptors located in the lungs work as an attachment point for COVID-19 which leads to coronavirus disease (COVID-19)-related pneumonia. Since ACE2 is found in cardiac tissues also, it causes acute myocardial injury and chronic damage to the cardiovascular system. So, particular attention should be given to cardiovascular involvement during treatment for COVID-19 infection especially those who are critically ill. In addition, further research is needed detailing the epidemiology, exact pathophysiological mechanism, treatment as well as short- and long-term prognosis in these patients.

Conflict of Interest: None

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