Review Article

Potential Adverse Effects of Coronavirus Disease 2019 on the Cardiovascular System

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Abstract

Coronavirus disease 2019 (COVID-19) has spread, at an unprecedented speed and scale, into a global pandemic, infecting more than 29 million cases worldwide across 215 countries and territories and killing more than 930,000 individuals. There is evidence that preexisting cardiac disease can render individuals vulnerable. A large number of patients with COVID-19 present with preexisting cardiovascular disease or develop new-onset cardiac dysfunction during the course of the illness. Therefore, particular attention should be given to cardiovascular protection during COVID-19 treatment. This review highlights recent advances in our understanding of the interaction between COVID-19 and the cardiovascular system, with special attention to the virological, pathological, and immunological characteristics of COVID-19, acute myocardial injury, myocarditis, arrhythmias, coronary artery disease, heart function, and the possible mechanisms.

Keywords: *Angiotensin-converting enzyme 2; Cardiovascular system; Comorbidity; Coronavirus; Coronavirus disease 2019; Heart injuries*

Introduction

Coronavirus disease 2019 (COVID-19), also known as the coronavirus pandemic, is an ongoing pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel enveloped RNA β-coronavirus [Figures 1 and 2] that has infected more than 29 million individuals worldwide across 215 countries and territories and has emerged as a major health crisis, resulting in over 930,000 deaths as of September 15, 2020.[1] The virus is spread primarily via small droplets from coughing, sneezing, and talking. The SARS-CoV-2 spike (S) protein uses angiotensin-converting enzyme 2 (ACE2) receptors to enter cells; the receptor-binding domains of SARS-CoV-2 S and SARS-CoV S bind with similar affinities to human ACE2 receptors, enabling the efficient spread of SARS-CoV-2 among humans. The SARS-CoV-2 S glycoprotein harbors a furin cleavage site at the boundary between the S_1/S_2 subunits, which is processed during biogenesis and sets this virus apart from SARS-CoV and SARS-related CoVs.[2] ACE2 is also expressed in the heart, providing a link between coronaviruses and the cardiovascular system.

Accumulating experience and research suggest that SARS-CoV-2 may preferentially infect older people and that patients with underlying medical problems, such as cardiovascular conditions, diabetes, chronic respiratory disease, and cancer, are more likely to develop serious illness and even death. Thus, the virus may directly or indirectly affect the heart and interact with cardiovascular medications.[3] In a large-scale report from the Chinese Center for Disease Control and Prevention (CDC), among a total of 72,314 case records (Box) from Hubei Province, with 44,672 confirmed cases of COVID-19 (62%), 16,186 suspected cases (22%), and 10,567 clinically diagnosed cases (15%), the overall case-fatality rate was 2.3%, which was elevated among those with preexisting comorbid conditions: 10.5% for cardiovascular disease (CVD), 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for

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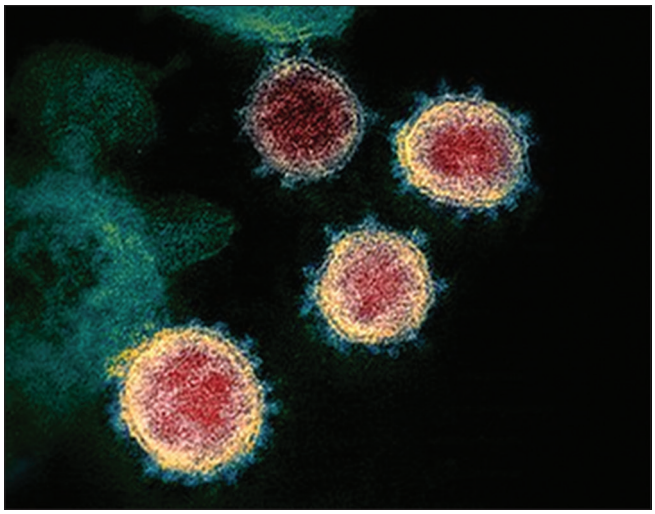

Figure 1: Electron micrograph of SARS-CoV-2 with its visible coronae.
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

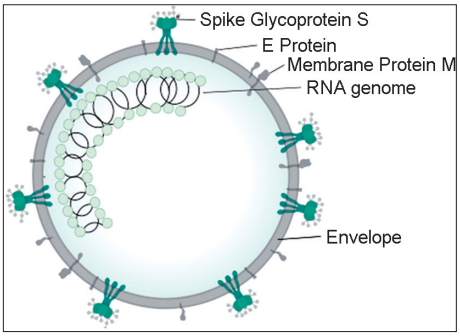

Figure 2: Structural view of a coronavirus.

cancer.[4] Therefore, particular attention should be given to cardiovascular protection during COVID-19 treatment. Furthermore, the best way to prevent and slow down transmission is to be well informed about the virus, the disease it causes, and how it spreads. Recommended preventive measures include hand washing, covering the mouth when coughing, social distancing, wearing a face mask in public, disinfecting surfaces, etc.

Although it is clear that a large number of patients with COVID-19 present with preexisting CVD or develop new-onset cardiac dysfunction during the course of the illness, much remains to be done and many questions remain unanswered. An adequate understanding of the interplay between COVID-19 and CVD is required for optimum management of such patients. In this report, we briefly review recent advances in our knowledge of coronaviruses, with an emphasis on their potential effects on the cardiovascular system.

Brief Summary of the Virological, Pathological, and Immunological Characteristics of Coronavirus Disease 2019

Virology

COVID-19 is caused by SARS-CoV-2, which is closely related to the original SARS-CoV and is thought to have a zoonotic origin. SARS-CoV-2 was isolated in environmental samples of the Huanan Seafood Market by the CDC.[5] Additionally, SARS-CoV-2 was first isolated in bronchoalveolar lavage fluid from three patients with COVID-19 from Wuhan Jinyintan Hospital on December 30, 2019.[6] The SARS-CoV-2 virion (genome size, 29.9 kb) possesses a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid protein. The virus particle has a diameter of 60-100 nm and appears round or oval. Based on genetic analyses, coronaviruses are genotypically and serologically divided into four subfamilies: α-, β-, γ-, and δ-CoVs. Human CoV infections are caused by α-and β-CoVs. SARS-CoV-2 is 96% identical at the whole genome level to other bat coronavirus samples (BatCov RaTG13). Based on sequence and evolutionary tree analysis, SARS-CoV-2 is considered to be a member of the β-CoV family.[7] Thus, SARS-CoV-2 belongs to the B lineage (sarbecovirus), which is a class of enveloped, positive-sense single-stranded RNA viruses with an extensive range of natural roots, and outside the human body, the virus can be killed by household soap [Figure 1].

Pathophysiology

The virus uses a special surface glycoprotein called a "spike" to connect to ACE2 receptors and enter the host cell.[8] ACE2 is a membrane-bound aminopeptidase that plays a vital role in the cardiovascular and immune systems. The lungs are the organ most affected by COVID-19 because ACE2 is most abundant in the type II alveolar cells of the lungs; as the alveolar disease progresses, respiratory failure might develop, followed by death. However, ACE2 is expressed in essentially all tissues, and its highest activity level is in the ileum and kidney, followed by adipose tissue, heart, brain stem, lung, vasculature, stomach, liver, and nasal and oral mucosa, based on activity data. ACE2 receptors are highly expressed in the heart and are involved in heart function and the development of hypertension and diabetes mellitus.[9] In animal models, ACE2 expression in the heart is an essential regulator of function, with ACE2 knockout mice developing severe left ventricular dysfunction.[10] Myocardial pericytes, which play an important role in maintaining the endothelial function, express ACE2 abundantly. Dysfunction in cardiac pericytes and endothelial cells, either due to direct infection or global inflammation, can lead to disruption

in the coronary microcirculation, with downstream ischemic consequences; however, its relationship with COVID-19 is purely conjectural.[11]

As yet, little data are available about the microscopic lesions and pathophysiology of COVID-19. The virus can cause acute myocardial injury and chronic damage to the cardiovascular system, which are more frequent in severe disease. Acute disease progression can be divided into three distinct phases: an early infection phase, a pulmonary phase, and a severe hyperinflammation phase. A systemic inflammatory response and immune system disorders are common during disease progression. Pro-inflammatory cytokines are upregulated in the lungs and other organs, and systemic inflammatory response syndrome provides a possible mechanism for multiorgan failure (usually involving the heart) in severe cases. COVID-19 may predispose patients to both venous and arterial thromboembolisms due to excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation.[12]

Immunopathology

SARS-CoV-2 has a tropism for ACE2-expressing epithelial cells of the respiratory tract. Patients with severe COVID-19 have symptoms of systemic hyperinflammation, with increased plasma concentrations of pro-inflammatory cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1, macrophage inflammatory protein-1α, and tumor necrosis factor (TNF)-α.[13-15] New evidence on T-cell immunopathology in patients with COVID-19 was reported by Diao *et al*. Their data point to significant T-cytopenia in circulating $CD4^+$ and $CD8^+$ T cells in patients with confirmed COVID-19. The serum of these patients had significantly elevated IL-6, IL-10, and TNF-a levels. Further analyses showed a progressive increase in $PD\text{-}1^+$ $CD8^+$ and $Tim\text{-}3^+$ $CD8^+$ subpopulations, as patients deteriorated from prodromal to symptomatic COVID-19 requiring intensive care.[16] Furthermore, patients with more severe conditions had higher IL-6 levels and activated $CD4^+$ and $CD8^+$ T cells, as suggested by higher expressions of CD69, CD38, and CD44. Additionally, higher percentages of checkpoint receptor $Tm3^+$ $PD\text{-}1^+$ subsets in $CD4^+$ and $CD8^+$ T cells showed that T cells were exhausted. NK group 2 member A, another marker of exhaustion, was elevated in $CD8^+$ T cells.[17]

Additionally, patients with COVID-19 have classical serum biomarkers of cytokine release syndrome, including elevated C-reactive protein, lactate dehydrogenase, D-dimer, and ferritin. Systemic inflammation results in vasodilation, allowing inflammatory lymphocytic and monocytic infiltration of the lung and heart [Figure 2].

Potential Adverse Effects of Coronavirus Disease 2019 on the Cardiovascular System

Patients with CVD appear to be at increased risk of severe manifestations of COVID-19, and 30%-35% of COVID-related deaths are caused by underlying CVD.[18] The impact of COVID-19 on the cardiovascular system may include primary or secondary cardiac involvement. Primary cardiac manifestations of COVID-19 include arrhythmias, acute coronary syndrome (ACS), and myocarditis. Secondary cardiac involvement is usually because of systemic inflammatory response syndrome and can manifest as acute myocardial injury/biomarker elevation and chronic heart failure.

Acute Myocardial Injury

Previous studies have confirmed that viral infections can cause myocarditis, induce myocardial infarction, aggravate heart failure, and significantly contribute to mortality.[19] In the past few months, accumulating clinical observations and studies have also found that COVID-19 may cause cardiovascular damage and increase CVD comorbidities. Elevated troponin levels are frequently seen in patients with COVID-19 and are associated with increased disease severity and risk of death. Reports suggest also that COVID-19 can cause acute cardiac complications. In various reports, an increase in high-sensitivity cardiac troponin I (hs-cTnI) was noted in 10%-20% of patients infected with COVID-19.[20] A small study by Huang *et al*. reported that acute myocardial injury appeared in 5 of the first 41 humans with detected SARS-CoV-2 in Wuhan, who mostly expressed increased hs-cTnI level (>28 pg/mL).[13] In the absence of a specific etiology, elevated troponin levels are likely due to myocardial injury from inflammation or a direct effect of SARS-CoV-2 infection. Between 7% and 27.8% of patients with COVID-19 may have elevated troponin levels.[21,22]

Shi *et al*. reported a cohort study of 416 consecutive hospitalized patients with confirmed COVID-19 (median age, 64 years; 50.7% female);[23] common symptoms included fever (80.3%), cough (34.6%), and shortness of breath (28.1%). Of the 416 patients, 82 (19.7%) had cardiac injury, and patients with cardiac injury were older, had more comorbidities, and higher C-reactive protein, procalcitonin, high-sensitivity troponin I, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels than those without cardiac injury. Furthermore, a greater proportion of patients with cardiac injury required noninvasive or invasive mechanical ventilation, complications were more common, and mortality was higher than in those without

cardiac injury. Overall, cardiac injury is a common condition among hospitalized patients with COVID-19 in Wuhan, China, and is associated with a higher risk of in-hospital mortality.[24]

Recently, Guo *et al*. reported a retrospective single-center case series of patients with COVID-19 at the Seventh Hospital of Wuhan.[25] Among 187 patients (mean age, 58.5 years) with confirmed COVID-19, 144 (77%) were discharged and 43 (23%) died. In total, 35.3% of patients had underlying CVD, including hypertension, coronary heart disease, and cardiomyopathy, and 27.8% of patients exhibited myocardial injury, as indicated by elevated troponin T (TnT) levels. The mortality during hospitalization was 7.62% in patients without underlying CVD and normal TnT levels, 13.33% in those with underlying CVD and normal TnT levels, 37.50% in those without underlying CVD but elevated TnT levels, and 69.44% in those with underlying CVD and elevated TnT levels. Plasma TnT levels demonstrated a high and significantly positive linear correlation with plasma high-sensitivity C-reactive protein and NT-proBNP levels. During hospitalization, patients with elevated TnT levels had more frequent malignant arrhythmias and greater glucocorticoid therapy and mechanical ventilation use than those with normal TnT levels. Thus, myocardial injury is associated with cardiac dysfunction and arrhythmias.[25] BNP levels were also elevated among intensive care unit (ICU) admissions in Washington and appeared to be more universal than troponin elevation.[26]

Myocarditis

In patients with severe COVID-19, SARS-CoV-2 appears to affect the myocardium and cause myocarditis, defined as myocardial injury and inflammation without an ischemic cause. This feature is consistent with the observed augmentation of inflammatory markers seen in case reports detailing myocarditis in COVID-19. The most frequent manifestation of cardiac involvement thus far appears to be myocarditis. Deng *et al*. reported on the first cohort of patients with COVID-19 and myocarditis.[27] Additionally, there are many such scattered case reports.[28-30] For example, Xu *et al*. reported on a 50-year-old male in Wuhan who died of confirmed COVID-19; biopsy samples were taken from the lung, liver, and heart tissue of the patient. Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates, the liver biopsy specimens showed moderate microvesicular steatosis, and there were a few interstitial mononuclear inflammatory infiltrates in the heart tissue.[31] Inciardi *et al*. reported on an otherwise healthy 53-year-old white woman without a history of CVD who tested positive for COVID-19 and was admitted to the cardiac care unit; examinations revealed increased NT-proBNP and high-sensitivity TnT levels, echocardiography changes, diffuse biventricular myocardial edema, and late gadolinium enhancement on cardiac magnetic resonance imaging. The patient was diagnosed with acute myocarditis complicated with cardiac insufficiency and was treated with inotropic support, antiviral drugs, corticosteroids, and chloroquine, with progressive stabilization in the clinical course.[32] Hu *et al*. reported on a 37-year-old male patient who was admitted to the hospital with chest pain and dyspnea for 3 days, accompanied by diarrhea; chest X-ray revealed significant enlargement of the heart; computed tomography indicated pulmonary infection, enlarged heart, and pleural effusion; electrocardiography suggested ST-segment elevation; and myocardial injury markers were significantly elevated (e.g., TnT, creatine kinase isoenzyme, and BNP), indicating acute myocardial injury. Furthermore, echocardiography revealed an enlarged heart and marked decrease in ventricular systolic function. After treatment, the patient's symptoms improved significantly.[33]

A recent case report by Tavazzi *et al*. suggested that the heart can be directly involved in the infection by SARS-CoV-2.[34] The authors described the first case of acute cardiac injury directly linked to myocardial localization of SARS-CoV-2 in a 69-year-old patient with flu-like symptoms that rapidly degenerated into respiratory distress, hypotension, and cardiogenic shock. The patient was successfully treated with venous-arterial extracorporeal membrane oxygenation (ECMO) and mechanical ventilation. Cardiac function was fully recovered in 5 days, and ECMO was removed. Endomyocardial biopsy demonstrated low-grade myocardial inflammation and viral particles in the myocardium, suggesting either viremia or infected macrophage migration from the lung.[34] Great vigilance is required, as some patients have presented without respiratory symptoms and were later found to be COVID-positive after being diagnosed with myocarditis.

Arrhythmias

Patients affected with COVID are at an increased risk of arrhythmias due to underlying comorbidities, polypharmacy, and disease progression, ranging from tachycardia and bradycardia to asystole. In most published studies, the specific cause or types of arrhythmias were not recorded; arrhythmias occur in approximately 14% of patients with COVID. Zhang *et al*. reported a retrospective, single-center case

series of 138 consecutive patients hospitalized at Zhongnan Hospital of Wuhan University with confirmed SARS-CoV-2-infected pneumonia (median age, 56 years; 54.3% men); of them, 10 patients (7.2%) had acute cardiac injury and 23 patients had arrhythmia (16.7%), with a higher prevalence among those requiring intensive care.[22] Seecheran *et al*. reported on a 46-year-old Caribbean-Black male presenting with COVID-19 with no significant medical history who experienced atrial arrhythmias (atrial flutter and atrial fibrillation).[35]

Elias *et al*. reported a set of observational studies from the United States; 1,258 adults with COVID-19 treated at three hospitals in New York in March and April 2020 were analyzed.[36] At 48 h, 73 patients (6%) had died and 174 (14%) were alive but receiving mechanical ventilation, and a total of 277 (22%) patients died by 30 days. Early development of respiratory failure was common, with 53% of all intubations occurring within 48 h of presentation. On multivariable logistic regression analysis, atrial fibrillation/flutter, right ventricular strain, and ST-segment abnormalities were found to be associated with death or mechanical ventilation at 48 h. The authors concluded that the combination of abnormal respiratory vital signs and electrocardiogram findings of atrial fibrillation/flutter, right ventricular strain, or ST-segment abnormalities accurately prognosticates early deterioration in patients with COVID-19 and may assist with patient triage.[36]

Furthermore, myocardial biomarkers should be evaluated in all patients with COVID-19 for risk stratification and prompt intervention. Patients with higher cTn levels have a significantly higher incidence of malignant arrhythmias than those with normal cTn levels (11.5% vs. 5.2%; $P < 0.001$).[37] Even after hospital discharge, myocardial injury might result in atrial or ventricular fibrosis, which is the substrate for subsequent cardiac arrhythmias. The extent of myocardial scarring, as assessed by cardiac magnetic resonance imaging, might be a powerful tool to better stratify the arrhythmic risk in patients recovered from COVID-19 who have evidence of myocardial injury at the time of infection. Additionally, the combination of multiple concurrent medications could potentially contribute to an increased arrhythmic risk. Several trials evaluating combination therapies are currently underway.

Coronary Artery Disease, Heart Failure, and Hypertension

Previous studies have suggested an association between influenza and acute myocardial infarction.[38-42] Although ACS and acute myocardial infarction are known to occur in patients with COVID-19, the incidence of such events is currently unclear. A case series from New York evaluated 18 patients with COVID-19 with ST-elevation myocardial infarction on electrocardiography; of these, 6 patients (33%) presented with chest pain, 14 (78%) had focal ST-segment elevation, 6 (35%) had a regional wall motion abnormality on transthoracic echocardiography, and 8 (44%) were clinically diagnosed as having myocardial infarction. Additionally, 9 patients (50%) underwent coronary angiography; of these, 6 (67%) showed obstructive disease.[43] Furthermore, a case report from Spain detailed the presentation of a 64-year-old male with no cardiovascular risk factors who presented with ACS following discharge from the hospital due to COVID-19 and underwent percutaneous coronary intervention.[44] In a case series of 18 patients, only 33% of patients with ST-elevation had chest pain and 72% died in the hospital.[43] Asif *et al*. reported on two patients admitted to the ICU with acute respiratory distress syndrome caused by COVID-19 who subsequently developed ST elevation and elevated troponins; the patients were treated conservatively, and these alterations resolved during their hospital stay.[45] Spontaneous coronary artery dissection has also been reported in the literature.

Thus, ACS is a recognized complication of COVID-19. Its pathophysiology may be related to the hypercoagulable state induced by the virus, causing thrombosis of the coronary arteries, as evidenced by significantly elevated D-dimer levels.[44] The higher thrombotic burden in the acute phase of COVID-19 relies on pro-inflammatory cytokine/chemokine release, increased endothelial dysfunction/damage, and potential sepsis-induced coagulopathy development in severe cases, all of which promote coagulation activation. Endothelial cell activation/damage due to the virus binding to the ACE2 receptor promotes acute inflammation and hypercoagulation. Chronic CVD may become unstable in the setting of SARS-CoV-2 infection due to imbalance between infection-induced increased metabolic demand and reduced cardiac reserve. Patients with coronary artery disease and heart failure may be at particular risk due to coronary plaque ruptures secondary to virally induced systemic inflammation. Pro-coagulant effects of systemic inflammation may increase the likelihood of stent thrombosis, and the assessment of platelet function and intensified antiplatelet therapy should be considered in those with a history of previous coronary intervention.

Several studies have identified heart failure as a significant manifestation of COVID-19. One of the first studies linking heart failure and COVID-19 involved 191 patients with COVID-19; 44 of these patients

developed heart failure, with a mortality rate of 64%. More than half of the reported deaths had heart failure as a predicting factor.[46] In a study by Ruan *et al*. of 68 fatal cases of COVID-19, 58% of patients died from respiratory failure, 7% from heart failure, and 33% from both respiratory and heart failure.[47] The development of new heart failure is not uncommon in patients with COVID-19. A small case series from the United States by Arentz *et al*. reported that 7 of 21 critically ill patients (33%) developed cardiomyopathies during the course of their ICU stay.[26] A multinational observational study demonstrated that COVID-19 complicated with heart failure was associated with an increased risk of in-hospital mortality.[48] Another report from the United States showed that congestive heart failure was an important comorbidity in patients who died due to SARS-CoV-2 infection, as well as a new-onset manifestation of the disease.[49] The possible mechanism of heart failure in patients with COVID-19 may be related to severe immune system over-reaction, resulting in a cytokine storm. The virus downregulates ACE2, leading to increased levels of angiotensin II, causing increased inflammation, hypertension, and thrombosis.[50]

Although hypertension is also considered as one of the most important risk factors for COVID-19, the relationship between hypertension and adverse outcomes remains uncertain. The prevalence of hypertension among patients with COVID-19 in various studies has ranged from 15% to 35%.[13,23,37,51-54] The average age was significantly higher in studies with an elevated prevalence of hypertension, which might be the main reason for the difference noted in the prevalence of hypertension among studies. Moreover, the impact of hypertension on the outcome and particularly, mortality in patients with COVID-19 is unclear due to a lack of data. In a systematic review and meta-analysis, Zuin *et al*. reported that hypertensive patients with SARS-CoV-2 infection had a significantly higher mortality risk than normotensive patients (odds ratio: 3.36, 95% confidence interval: 1.96–5.74, $P < 0.001$).[55] Thus, at present, existing data suggest that the prevalence of hypertension in patients with COVID-19 with a fatal outcome is high; however, whether hypertension is a predictor of mortality independently of other cardiovascular risk factors (age, obesity, diabetes) and comorbidities remains under debate.[21,48]

Furthermore, a recent propensity-adjusted retrospective study of 1128 patients with hypertension and COVID-19 demonstrated a reduced mortality rate in patients under ACE inhibitor (ACE-I) and angiotensin receptor blocker (ARB) therapies.[56] Therefore, several societies have suggested that patients continue their current ACE-I and ARBs therapies.[57] To date, studies have not provided evidence that renin-angiotensin-aldosterone system (RAAS) inhibitors should be avoided or switched in patients with COVID-19.

Role of Preexisting Cardiovascular Disease, Cardiovascular Disease Risk Factors, Cardiovascular Disease Comorbidity, and the Long-term Impact

Patients with preexisting CVD appear to have heightened vulnerability to developing COVID-19 and tend to have more severe disease, with worse clinical outcomes. Various cardiovascular risk factors also adversely affect the prognosis of patients with COVID-19. A meta-analysis from China comprising 1,527 patients with COVID-19 reported a prevalence of 9.7%, 16.4%, and 17.1% for diabetes, cardio-cerebrovascular disease, and hypertension, respectively.[13,19,58] More importantly, the presence of diabetes, cardio-cerebrovascular disease, and hypertension was associated with a 2-fold, 3-fold, and 2-fold greater risk of severe disease or ICU admission, suggesting a prognostic impact of these comorbidities. A larger report from the CDC described clinical outcomes in 44,672 confirmed cases of COVID-19; the overall case fatality rate was 2.3% in the entire cohort but was significantly higher in patients with hypertension, diabetes, and CVD (6%, 7.3%, and 10.5%, respectively).[4] Zhou *et al*. reported a retrospective, multicenter cohort study comprising 191 patients; among these, 91 (48%) had a comorbidity, with hypertension as the most common comorbidity (58 patients, 30%), followed by diabetes (36 patients, 19%) and coronary heart disease (15 patients, 8%).[48] An analysis of 3,200 mortality cases from 19 regions in Italy as of March 20, 2020, demonstrated that patients who died were largely older individuals with an average of 2.7 comorbidities; overall, 1.2% of the deceased patients had no comorbidities, 23.5% had 1 comorbidity, 26.6% had 2 comorbidities, and 48.6% had 3 or more comorbidities. With respect to CVD risk factors, ischemic heart disease was present in 30.1%, atrial fibrillation in 22.0%, stroke in 11.2%, hypertension in 73.8%, and diabetes in 33.9% of patients. Comparable data were also published from the Lombardy ICU Network, which included 1,591 critically ill patients (mean age, 63 years) from 72 hospitals.[59]

A case series study from the United States (21 patients; mean age, 70 years) reported that diabetes and congestive heart failure were present in 33.3% and 42.9% of patients, respectively; furthermore, acute cardiac dysfunction occurred in 33.3% of patients, and 52.4% patients died.[26]

A recent study from Italy by Inciardi *et al*. evaluated 99 consecutive patients hospitalized due to COVID-19 pneumonia; of these patients, 53 with a history of cardiac disease and 46 without cardiac disease were compared; the authors found that patients with concomitant cardiac disease had an extremely poor prognosis than those without a history of cardiac disease, with higher rates of mortality, thromboembolic events, and septic shock.[60] An analysis of an outpatient and inpatient cohort of 1,099 patients with COVID-19 determined that patients with severe disease had an increased rate of any coexisting disorders (38.7% vs. 21.0%), diabetes (16.2% vs. 5.7%), hypertension (23.7% vs. 13.4%), coronary artery disease (5.8% vs. 1.8%), and cerebrovascular disease (2.3% vs. 1.2%).[54]

Determining the potential long-term consequences of COVID-19 requires careful follow-up of those recovering from current COVID-19 and is important for understanding the long-term impact of this illness and to protect these patients from developing future CVD.

Cardiovascular Pathology

Recently, Dutch scholars reported a systematic review of pathological findings in COVID-19, which included 42 articles comprising 198 individual cases.[61] Gross examination of the heart was performed in 51 cases. Aside from mild pericardial edema and some serosanguinous pericardial effusion, there were no notable abnormalities, other than findings expected based on preexisting conditions, such as coronary heart disease (in 29 cases). Microscopic analyses of cardiac tissue (performed in 49 cases) revealed that apart from preexisting pathologies such as myocardial hypertrophy, atherosclerosis, and general interstitial fibrosis, 5 cases had mild myocardial edema and 1 case had atypical interstitial fibrosis. Furthermore, low-grade interstitial infiltration of mononuclear cells was present in 9 cases, whereas signs of lymphocytic myocarditis were observed in 2 cases.[61]

Possible Mechanisms of Adverse Effects of Coronavirus Disease 2019 on the Cardiovascular System

COVID-19 can cause cardiac injury, and many patients with COVID-19 have underlying CVD or develop acute cardiac injury during the course of the illness. Clearly, people are also very concerned with the potential chronic and long-term effects of COVID-19 on the cardiovascular system. The pathophysiological mechanisms underlying myocardial injury caused by COVID-19 are not yet well known, and more studies are needed to further delineate the mechanisms. However, based on current data, the following potential mechanisms may responsible for cardiovascular complications in COVID-19 [Figures 3 and 4].

Direct myocardial injury

ARS-CoV-2 enters human cells by binding to receptors for ACE2, which plays an important role in the neurohumoral regulation of the cardiovascular system in normal health, as well as in various disease conditions. The binding of SARS-CoV-2 to ACE2 receptors can result in the alteration of ACE2 signaling pathways, leading to acute myocardial and lung injury.[58,62] Additionally, disruption of ACE2 leads to age-dependent cardiomyopathy, cardiac dysfunction, and heart failure.[10] Collectively, based on the significant resemblance of SARS-CoV infection with SARS-CoV-2 infection, the possible mechanisms of myocardial injury in COVID-19 include direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon-mediated immune response, exaggerated cytokine response (in addition to coronary plaque destabilization), and hypoxia.

Altered myocardial demand-supply ratio

Unquestionably, the disparity between augmented metabolic demand and reduced cardiovascular reserve is a possible mechanism of cardiovascular complications in COVID-19. Increased cardiometabolic demand associated with the systemic infection, coupled with hypoxia caused by acute respiratory illness, can impair the myocardial oxygen demand-supply relationship and lead to acute myocardial injury.[63] Viral infections may increase metabolic demands by four-to eight-fold over the normal physiological workload of the heart. This, in addition to the possible direct effects of pneumonia, can impair cardiac function.[64]

Systemic inflammation

Severe forms of COVID-19 are characterized by acute systemic inflammatory response and a cytokine storm, which can result in injury to multiple organs.[13,60] Although the lungs are considered as the main target organ of SARS-CoV-2, the virus can affect many other organs, including the heart, blood vessels, kidneys, gut, and brain, via various mechanisms.[65] It has been widely proposed that one of the ways SARS-CoV-2 can critically affect these organs is through an intense inflammatory reaction.

Dysfunctional coagulation and venous and arterial thromboembolism

COVID-19 involves potentially deleterious processes in hemostasis/coagulation and the inflammation system. Patients with COVID-19 may be predisposed to both venous and arterial thromboembolic disease due to

excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation.[51,54] Dysfunctional coagulation is an important risk factor accountable for a high risk of severe disease and death. Abnormal activation of the renin-angiotensin system and systemic endotheliitis caused by ACE2 dysfunction, the innate immune response and inflammation activation participate in dysfunctional coagulation. The interaction of endothelial cell dysfunction with inflammation due to SARS-CoV-2 infection may lead to abnormal coagulation and sepsis, indicating a poor prognosis in patients with COVID-19.[66] Increased coagulation eventually causes multiorgan thromboembolism and death.[67] Considerable evidence shows that patients with COVID-19 manifest abnormal coagulation in terms of both clinical presentation and laboratory examinations.[68,69] Thrombosis and pulmonary embolisms have been observed in severe cases, in line with the finding of elevated D-dimer and fibrinogen levels in such cases. Microvascular permeability due to endothelial injury can facilitate viral invasion. Precise knowledge of the incidence of thrombotic complications in patients with COVID-19 is important for decision-making with regard to the intensity of thromboprophylaxis. Plaque ruptures and coronary thrombosis-systemic inflammation, as well as increased shear stress due to increased coronary blood flow, can precipitate plaque ruptures, resulting in acute myocardial infarction. The prothrombotic milieu created by systemic inflammation further increases the risk.

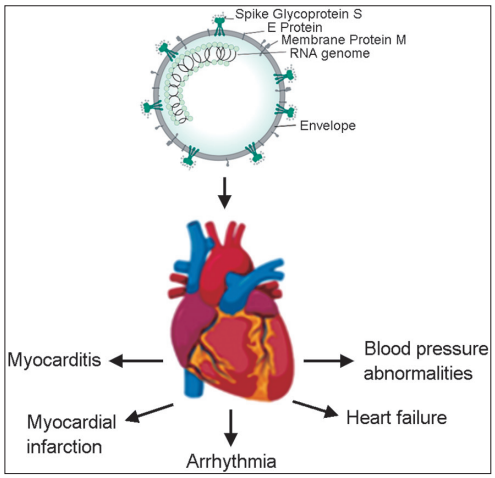

Figure 3: Possible adverse effects of COVID-19 on the cardiovascular system.

COVID-19: Coronavirus disease 2019

Electrolyte imbalances

Electrolyte imbalances can occur in any critical systemic illness and precipitate arrhythmias. Hypokalemia in COVID-19 (due to the interaction of SARS-CoV-2 with RAAS) increases vulnerability to various tachyarrhythmias.[70] Patients with COVID-19 are at

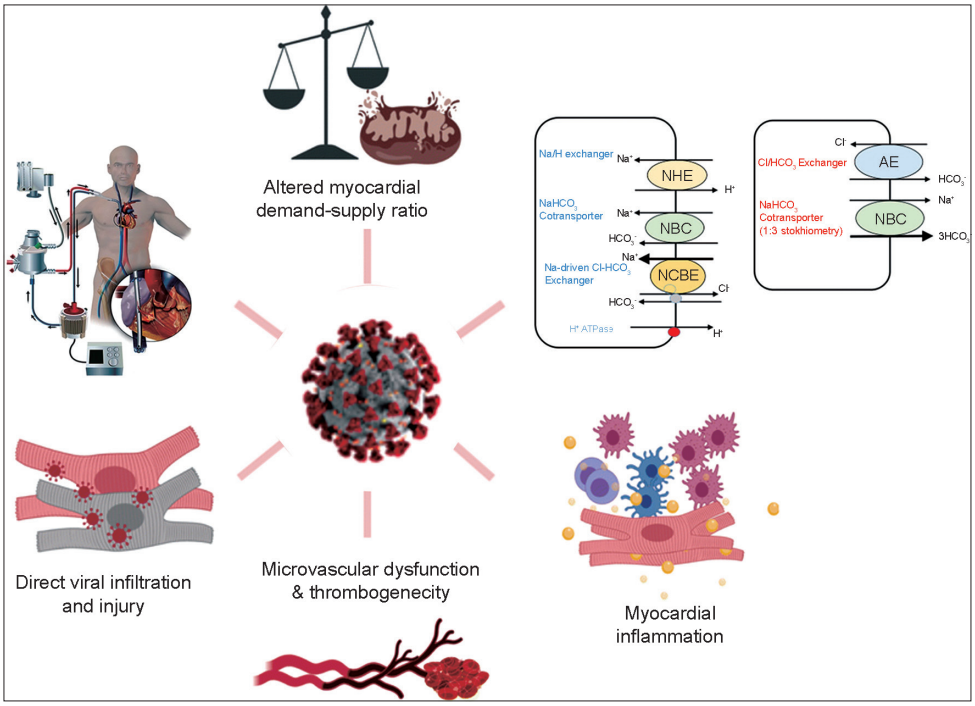

Figure 4: Possible mechanisms of the adverse effects of COVID-19 on the cardiovascular system.

COVID-19: Coronavirus disease 2019, AE: anion exchanger, NHE: Na^+/H^+ exchange, NBC: Na^+–HCO_3^- cotransport, NCBE: sodium-driven chloride bicarbonate

risk of arrhythmia, at least partially because of the high incidence of hypokalemia. SARS-CoV-2 invades cells by binding to ACE2 receptors, which can enhance urinary potassium excretion due to the increased availability of angiotensin II.[70]

Adverse effects of various therapies

Although there are no approved medications or vaccines for the treatment of COVID-19, and approved specific antiviral drugs against SARS-CoV-2 are still lacking, a large number of existing drugs, including traditional Chinese medicines, are being explored as possible treatments for patients with COVID-19. Recent publications have suggested the use of chloroquine and its derivative, hydroxychloroquine, as a treatment for COVID-19.[71-73] Many antiviral drugs, antibiotics, and glucocorticoids have some side effects, and even deleterious effects, on the cardiovascular system. Therefore, special attention must be paid to the side effects caused by various therapies.[74]

The RAAS system is widely implicated in diabetes, hypertension, and heart failure. Furthermore, ACE-I and ARB drugs, based upon strong efficacy data, are commonly used in the management of hypertension, heart failure, and postmyocardial infarction care and to slow the progression of renal disease associated with diabetes. A retrospective study found that ACE-I/ARB users have a lower all-cause mortality rate than nonusers (adjusted hazard ratio: 0.37, 95% confidence interval: 0.15-0.89, $P = 0.03$).[56] Thus far, there is a lack of scientific evidence and clinical data to support the discontinuation of ACE-I/ARB use in patients with COVID-19 and coexisting heart failure, hypertension, or ischemic heart disease. The well-studied reduction in mortality conferred by ACE-I/ARB use and the beneficial effects in patients with diabetes, chronic kidney disease, and proteinuria or albuminuria currently outweigh the theoretical risks.[75,76]

Summary and Future Directions

COVID-19, caused by SARS-CoV-2, has resulted in considerable morbidity and mortality worldwide. The literature to date suggests that a large number of patients with COVID-19 with preexisting CVD or the development of new-onset cardiac dysfunction during the course of the illness may have significantly worse outcomes and an increased risk of death. Therapies under investigation for COVID-19 may have cardiovascular side effects. The use of cardiac-specific biomarkers (e.g., troponin and NT-proBNP) has shown prognostic value, with elevated levels linked to an increased incidence of mortality, which can ultimately result in a more rapid escalation in treatment. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19. Understanding the interplay between COVID-19 and the cardiovascular system and identifying the risk factors for the development of cardiac complications are important and meaningful. Robust epidemiologic and biologic studies are urgently needed to better understand the mechanisms underlying these associations to develop better therapies. A large number of prospective randomized controlled trials and cohort studies are currently ongoing worldwide.

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Conflicts of interest

Bing-Yin Wang is the Board member of the journal.

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