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Review

Review

Cardiovascular disease in patients with COVID-19: evidence from cardiovascular pathology to treatment

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Abstract

The coronavirus disease-2019 (COVID-19) caused by the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has rapidly developed into a global pneumonia pandemic. At present, COVID-19 has caused more than 70,000,000 confirmed cases with over 1,500,000 deaths worldwide, as reported by WHO. Cardiovascular disease is the major comorbidity of COVID-19 patients and is closely related to the severity of COVID-19. SARS-CoV-2 infection can directly or indirectly cause a series of cardiac complications, including acute myocardial injury and myocarditis, heart failure and cardiac arrest, arrhythmia, acute myocardial infarction, cardiogenic shock, Takotsubo cardiomyopathy, and coagulation abnormalities. Intensive research on the SARS-CoV-2-associated cardiovascular complications is urgently needed to elucidate its exact mechanism and to identify potential drug targets, which will help to formulate effective prevention and treatment strategies. Hence, this review will summarize recent progress regarding the effects of COVID-19 on the cardiovascular system and describe the underlying mechanism of cardiovascular injury caused by SARS-CoV-2.

Key words: COVID-19, SARS-CoV-2, cardiovascular disease, cardiovascular injury, treatment

Introduction

Coronaviruses (CoVs) belong to the subfamily Coronavirinae in the family Coronaviridae and the order Nidovirales and can be divided into four genera: *Alpha-coronavirus* (α-CoV), *Beta-coronavirus* (β-CoV), *Gamma-coronavirus* (γ-CoV), and *Delta-coronavirus* (δ-CoV) [1,2,3]. It is known that only α-CoV and β-CoV can infect humans. In the past two decades, two outbreaks of atypical pneumonia caused by β-CoVs (SARS-CoV and MERS-CoV) were severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS) [4,5]. Since the end of December 2019, an outbreak of novel coronavirus pneumonia was first reported in Wuhan city, Hubei Province, China, but the original source of the virus is not yet known. This newly emerged SARS-CoV-2 belongs to the β-CoV lineage B and is closely related to the SARS-CoV. It has been found that the genome sequence of SARS-CoV-2 shares more than 80% identical to those of SARS-CoV and bat SARS-like coronavirus [6,7]. Thus, it is believed that SARS-CoV-2 originates from bats and may infect humans through an unknown intermediate host.

Coronavirus disease 2019 (COVID-19) has rapidly developed into a pandemic. Cardiovascular comorbidities are common in patients infected with SARS-CoV-2. The infection of SARS-CoV-2 can directly or indirectly cause cardiovascular injury in COVID-19 patients. In addition, some antiviral drugs used for the treatment of COVID-19 have potential side effects on the cardiovascular system. These factors may lead to a significant increase in mortality rate in patients with COVID-19. Thus, it is necessary to attach great importance to cardiovascular complications in COVID-19 patients.

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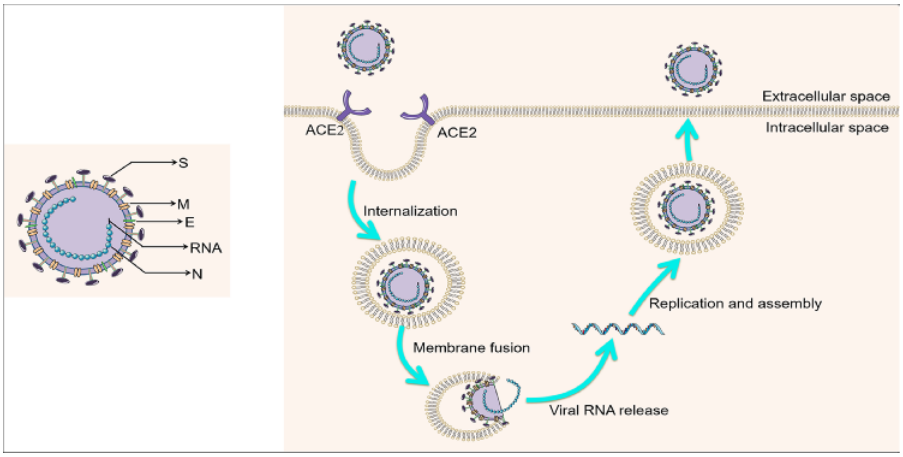

Figure 1. SARS-CoV-2 infects cardiomyocytes through the receptor ACE2 (A) Structure of SARS-CoV-2. Four structural proteins are as follows: spike protein (S-purple), nucleocapsid protein (N-blue), membrane protein (M-orange), and envelope protein (E-green). (B) SARS-CoV-2 enters cardiomyocytes through the receptor ACE2 and then undergoes internalization, membrane fusion, viral RNA release, replication, and assembly, thus completing the life cycle.

In this review, we describe the impacts of COVID-19 on the cardiovascular system, the underlying mechanism of cardiovascular injury caused by SARS-CoV-2, and therapeutic strategies for cardiovascular complications in patients with COVID-19.

Structure and Genome of SARS-CoV-2

The SARS-CoV-2 genome (29,870 bp, excluding the poly (A) tail) is an enveloped, positive single-stranded RNA virus that includes 14 open reading frames (ORFs). The first two ORFs, ORF1a and ORF1b, representing approximately 67% of the entire genome that encodes 16 nonstructural proteins, while the remaining ORFs encode four structural proteins and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14) [8–10]. The four structural proteins are the spike surface glycoprotein (S), nucleocapsid protein (N), envelope protein (E), and membrane protein (M), which are essential for the assembly and infection of SARS-CoV-2. Homotrimers of S proteins make up the distinctive spike structure on the surface of the virus, which is crucial for mediating receptor recognition and membrane fusion [11,12]. Notably, angiotensin-converting enzyme II (ACE2) serves as a key receptor that mediates the entry of SARS-CoV-2 into the host cell [13–15]. During viral infection, the trimeric S protein can be further cleaved by a host cell furin-like protease into S1 and S2 subunits. S1 contains a receptor-binding domain that directly binds to the peptidase domain of ACE2, while S2 is responsible for membrane fusion [16–18] (**Fig. 1**). Wrapp *et al.* [19] revealed that the binding affinity of SARS-CoV-2 spike protein to ACE2 is approximately 10- to 20-fold higher than that of SARS-CoV, making it easier to spread from human to human. ACE2 is widely distributed and is expressed in abundance in the lungs, blood vessels, and heart [20–22], suggesting that SARS-CoV-2 could infect the cardiovascular system by the human receptor ACE2.

Impact of COVID-19 Infection on the Cardiovascular System

Apart from respiratory symptoms, many patients have cardiovascular symptoms, such as heart palpitations and chest tightness/pain, as the initial clinical manifestation of COVID-19 [23–27]. Moreover, several studies also showed that COVID-19 can exacerbate preexisting cardiovascular disease and/or cause new cardiovascular injuries [28,29]. COVID-19 patients with underlying cardiovascular diseases (hypertension, coronary heart disease, heart failure, *etc.*) displayed more severe clinical outcomes and higher mortalities [30–32]. These clinical findings indicated pronounced cardiovascular sequelae for SARS-CoV-2 infection. Therefore, it is important to identify cardiac-related manifestations in patients with COVID-19. The causal association between COVID-19 and cardiovascular abnormities is summarized in **Fig. 2**.

Acute myocardial injury and myocarditis

Acute myocardial injury can be caused by myocarditis and myocardial ischemia, which is mainly manifested by elevated troponin levels [33,34]. Ruan *et al.* [28] reported that SARS-CoV-2 infection can trigger fulminant myocarditis, resulting in acute myocardial injury in patients with COVID-19. Myocardial injury has also been described in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, China, with elevated serum high-sensitivity cardiac troponin I (hs-cTnI) levels (>28 ng/l) [35]. In this study, four of five patients with myocardial injury were admitted to the intensive care unit (ICU), accounting for 31% of the total number of ICU patients. Moreover, the mean systolic blood pressure in ICU patients was 145 mmHg, which was significantly higher than that of non-ICU patients (122 mmHg) [35]. Another report of 150 patients with COVID-19 in Wuhan, including 126 mild cases and 24 severe cases, showed that N-terminal pro-B-type natriuretic peptide, hs-cTnI, high-sensitivity CRP, and serum creatinine levels were higher in severe cases than in mild cases [36]. In addition, Wang *et al.* [37] reported a single-center case series of 138 hospitalized patients with COVID-19 in Wuhan, of which 36 patients with severe symptoms were treated in the ICU. The levels of myocardial injury biomarkers (hs-cTnI and creatine kinase) were markedly higher in ICU/severe cases than in their non-ICU counterparts [37]. Taken together, these studies suggest that the severity of COVID-19 is implicated in the occurrence of acute myocardial injury. It is therefore essential to monitor and manage myocardial injury in patients with severe COVID-19.

Heart failure and cardiac arrest

Virus infection is an important cause of aggravating heart failure or inducing acute heart failure. Previous reports have suggested that

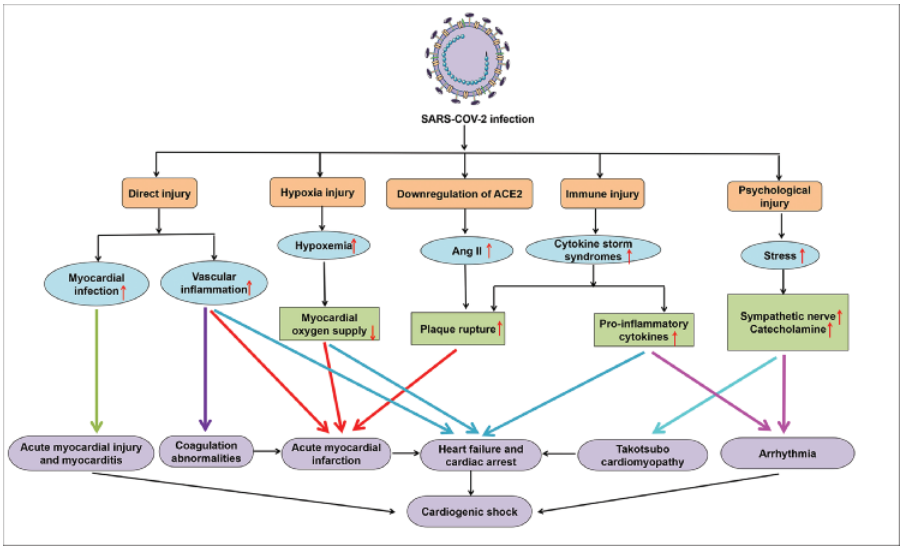

Figure 2. Schematic diagram of the underlying mechanism of cardiovascular injury caused by SARS-CoV-2 infection SARS-CoV-2 infection can cause cardiovascular injury through multiple mechanisms, including direct injury, downregulation of ACE2, immune injury, hypoxia injury, and psychological injury.

SARS-CoV and MERS-CoV infection can cause or aggravate heart failure [38–40]. Recently, a clinical study of 99 cases with confirmed COVID-19 from Wuhan showed that 11 (11%) patients had died of which 2 patients had no previous history of chronic heart disease but developed heart failure and eventually died of a sudden cardiac arrest [27]. Additionally, Chen *et al.* [26] reported that cardiac complications were observed more frequently in 113 deceased patients with COVID-19, including acute cardiac injury (72/94; 77%) and heart failure (41/83; 49%). Furthermore, regardless of the history of cardiovascular disease, heart failure is a common cardiac complication in deceased patients [26]. For heart failure reported in these articles, the possibility of right heart failure and associated pulmonary hypertension should be considered. Lung involvement in patients with COVID-19 can cause ventilation–perfusion mismatch and a decrease in pulmonary vascular beds. Then, microvascular occlusion and reduced functional residual capacity increase pulmonary vascular resistance, resulting in pulmonary hypertension and right heart failure. In order to reduce case fatality rate, it is necessary to attach great importance to the treatment and prevention of heart failure in patients with COVID-19.

Arrhythmia

Arrhythmias are common cardiac manifestations described in COVID-19 patients. It has been reported that a 55-day-old female infant infected with SARS-CoV-2 had tachycardia (150–170 beats per minute) [41]. Heart palpitations were also reported to be one of the initial symptoms in some patients with COVID-19 [25], which indicates the possibility of arrhythmia caused by SARS-CoV-2 infection. Moreover, a report of 138 hospitalized patients with COVID-19 in Wuhan, China, showed that 23 patients had arrhythmias, of which 16 (44.4%) were admitted to the ICU [37]. In addition, Cao *et al.* [42] also reported that patients with COVID-19 in ICU were more likely to suffer from arrhythmia (ICU 38.9% vs non-ICU 13.1%). These studies suggest that arrhythmia is one of the important cardiac complications in patients with severe COVID-19. However, the types of arrhythmia and specific ECG changes in COVID-19 patients have not been published or presented. Of note, arrhythmia can occur in patients with COVID-19, but the manifestations related to arrhythmia may be masked by respiratory symptoms. Therefore, patients with severe COVID-19 should be closely monitored for paroxysmal tachycardia or increased pulse rate that does not match the disease status.

Acute myocardial infarction

Acute myocardial infarction is a critical manifestation of coronary heart disease and has been reported as a common cardiac complication in patients with viral pneumonia [43–45]. Recently, a retrospective cohort study of 191 patients with confirmed COVID-19 showed that 15 (8%) patients had coronary heart disease [29]. Data from the National Health Commission of China showed that 17% of patients diagnosed with COVID-19 had coronary heart disease [46]. Notably, several studies showed that patients with severe COVID-19 had increased coagulation activity, marked by elevated D-dimer concentrations (>1 g/l) [26,29]. Local inflammation, induction of procoagulant factors, and hemodynamic changes may increase the risk of atherosclerotic plaque rupture, resulting in acute myocardial infarction. Thus, the highly contagious COVID-19 pneumonia may be closely related to the occurrence of acute myocardial infarction.

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy, also called stress-induced cardiomyopathy, is a clinical syndrome characterized by acute and transient regional left ventricular systolic dysfunction usually triggered by physical or emotional stressors including infections [29,47]. The COVID-19 pandemic has caused an unprecedented health crisis, leading to anxiety, distress, and fear, with emerging cardiovascular implications. Several studies have noted the occurrence of Takotsubo cardiomyopathy in patients infected with COVID-19. In a retrospective cohort study involving 1914 patients with COVID-19, the incidence of Takotsubo cardiomyopathy increased significantly by 7.8% during the COVID-19 pandemic, compared with prepandemic incidences that ranged from 1.5% to 1.8% [48]. Meanwhile, among 21

patients with severe COVID-19, seven (33.3%) patients developed dilated cardiomyopathy, characterized by reduced left ventricular systolic function, without a past history of systolic dysfunction [49]. In addition, a number of the drugs used in COVID-19 may also cause cardiomyopathy, including IFN, bevacizumab, and chloroquine [50,51]. Thus, the current pandemic scenario of COVID-19 may represent an important trigger for Takotsubo cardiomyopathy, not only due to the respiratory infection, but by the profound psychological and emotional stress caused by the isolation period resulting in an excessive release of catecholamines.

Coagulation abnormalities

Patients with COVID-19 are more likely to have an elevated risk of arterial and venous thromboembolism due to a state of endothelial dysfunction, vascular inflammation, and hypercoagulability associated with SARS-CoV-2 infection [52]. Abnormal coagulation parameters, such as prothrombin time, fibrin degradation products, activated partial thromboplastin time, and D-dimer, were noted in patients with COVID-19. In particular, increased levels of fibrin degradation products and D-dimer were suggested to be closely associated with poor prognosis [52,53]. In an early report involving 1099 patients with COVID-19 from China, 46% of patients had elevated D-dimer levels (>0.5 mg/l) (60% of those with severe illness) [54]. Moreover, another report showed that fibrin degradation products and D-dimer levels were significantly higher in COVID-19 non-survivors compared to survivors, and 71.4% of non-survivors met clinical criteria for disseminated intravascular coagulation during the course of their disease [53]. Similarly, a small observational study involving 184 critically ill patients with COVID-19 revealed a 31% incidence of radiologically confirmed thrombotic complications (4% arterial and 27% venous) [55]. In addition, levels of factor VIII and fibrinogen were elevated in COVID-19 patients, suggesting a hypercoagulable state [56,57]. These studies suggest that a substantial proportion of patients with COVID-19 have coagulation abnormalities, which may contribute to the development of multiple cardiovascular manifestations of COVID-19.

Cardiogenic shock

Cardiogenic shock has been reported as a late complication of COVID-19. In seven patients with confirmed COVID-19, new-onset biventricular failure and vasoplegia were noted, prior to the development of severe cardiogenic shock [58]. Tavazzi *et al.* [59] reported a case of acute cardiac injury directly linked to myocardial localization of SARS-CoV-2 in a 69-year-old patient with flu-like symptoms rapidly degenerating into cardiogenic shock. Cardiogenic shock may be an uncommon but life-threatening complication of a SARS-CoV-2 infection. In a study by Yu *et al.* [60] among 226 patients admitted to an ICU for severe COVID-19, three (1.3%) patients developed cardiogenic shock. Besides, cardiogenic shock is often mixed with other types of shock following SARS-CoV-2 infection, such as vasoplegic shock [58,61]. Of note, circulatory and respiratory support with a combination of extracorporeal membranous oxygenation (ECMO) and percutaneous ventricular assist device should be considered in COVID-19 patients with a combined cardiogenic and vasoplegic shock.

Characteristics of Cardiovascular Pathology in Patients with COVID-19

Recently, by obtaining biopsy samples at autopsy, Xu *et al.* [62] investigated the pathological characteristics of the first patient who died from severe COVID-19. It was found that the pathological features of COVID-19 are related to myocardial inflammation and damage. The heart biopsy specimens of the patient with COVID-19 showed degeneration and necrosis of myocardial cells. Moreover, there were a few interstitial inflammatory infiltrates in the heart tissue, including monocytes, lymphocytes, and neutrophils [62]. In addition, if patients infected with COVID-19 have the underlying cardiovascular diseases (hypertension, coronary heart disease, *etc.*), the pathological characteristics may include vascular endothelial cell shedding, endovascular inflammation, and thrombosis. Notably, patients with COVID-19 have a large amount of mucus exudation in the lungs, which may affect heart function. Whether this has a specific effect on cardiovascular pathology needs further investigation. Taken together, understanding the characteristics of cardiovascular pathology in patients with COVID-19 may help provide new insights into the pathogenesis of cardiovascular disease caused by SARS-CoV-2 infection, which may help physicians to formulate a timely strategy for the treatment of patients with cardiovascular complications and to reduce mortality.

Mechanisms of Cardiovascular Injury in Patients with COVID-19

The mechanisms of cardiovascular injury caused by SARS-CoV-2 infection have not been fully elucidated, but it is speculated that SARS-CoV-2 affects the cardiovascular system through multiple mechanisms, including direct injury, downregulation of ACE2, immune injury, hypoxia injury, and psychological injury.

Direct injury

Although CoVs usually infect the respiratory tract, shedding of the virus in plasma or serum is common. Several studies showed that SARS-CoV-2 viral RNA is readily detected in the blood [63–65]. Importantly, the presence of viral RNA in the blood is positively correlated with COVID-19 severity [63]. Therefore, SARS-CoV-2 can directly infect cardiomyocytes through blood circulation. Direct SARS-CoV-2 infection can trigger inflammation, apoptosis, and necrosis of cardiomyocytes, thereby resulting in acute myocardial injury and myocarditis.

Downregulation of ACE2

The renin-angiotensin system (RAS) has been implicated in the development of cardiovascular disease. ACE2, a pivotal component of the RAS, was first discovered in 2000 [66]. ACE2, the first known human homologue of ACE, catalyzes the cleavage of Angiotensin I (Ang I) to Ang 1–9 and Ang II to Ang 1–7, the latter has beneficial effects on cardiovascular diseases, such as improving heart function, regulating blood pressure, and resisting atherosclerosis [67–71]. Therefore, ACE2 protects the cardiovascular system by degrading Ang II and increasing Ang 1–7. It is noteworthy that ACE2 is also an important target for SARS-CoV and SARS-CoV-2 infections. It has been reported that mice infected with human SARS-CoV trigger an ACE2-dependent myocardial infection with a significant reduction in ACE2 expression [72]. The presence of SARS-CoV in the hearts of deceased patients was also associated with a marked decrease in ACE2 protein expression [72], suggesting a key role of ACE2 in mediating SARS-CoV infection in the heart. Besides, SARS-CoV infection and the spike protein of SARS-CoV were found to reduce ACE2 expression and elevate Ang II levels [73,74], thereby increasing the risk of cardiovascular events. Recently, several studies showed that SARS-CoV-2 infection, expression, and replication

are also closely related to its host cell receptor ACE2 [75,76]. The plasma levels of Ang II from SARS-CoV-2-infected patients were significantly elevated and linearly associated with viral load [77]. Therefore, the downregulation of ACE2 expression by SARS-CoV-2 infection may be an important cause of cardiovascular injury.

Immune injury

The immune response is likely to be highly involved in the process of SARS-CoV-2-related cardiac injuries. Upon entry into cardiomyocytes, SARS-CoV-2 rapidly replicates and triggers a strong immune response, which results in cytokine storm syndromes and heart tissue damage. Cytokine storm syndromes, also known as hypercytokinemia, are a group of disorders featured by excessive activation of T cells and uncontrolled production of pro-inflammatory cytokines largely due to viral infections [78–80]. Recently, accumulating evidence suggests that a number of patients with severe COVID-19 may have a cytokine storm syndrome, represented by elevated plasma levels of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6, IL-8, IL-12, MCP1, *etc*.) [27,35,81,82]. Moreover, Xu *et al*. [62] reported that CD4 and CD8 T cells in peripheral blood of patients with COVID-19 were over-activated, as manifested by the high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. In addition, the concentration of pro-inflammatory CCR4+CCR6+Th17 is high in CD4 T cells [62]. These studies suggest severe immune injury caused by SARS-CoV-2 infection. Notably, cytokine storm syndromes trigger rupture or erosion of coronary plaques, thereby resulting in acute myocardial infarction and ventricular dysfunction [83–87]. Previous studies have revealed that patients with SARS have substantial left ventricular dysfunction due to the cytokine storm resulting from an overaggressive host immune response to SARS-CoV infection [88]. Therefore, SARS-CoV-2 infection can cause cardiovascular injury by inducing immune injury and cytokine storm.

Hypoxia injury

Hypoxemia is a common clinical manifestation of cardiac and pulmonary diseases. Numerous studies have shown that patients with severe COVID-19 have hypoxemia [54,89–91]. These critically ill patients usually require oxygen therapy, mechanical ventilation, and ECMO for respiratory support therapy. Thus, severe pneumonia caused by SARS-CoV-2 infection may impair gas exchange, eventually resulting in hypoxemia. SARS-CoV-2 infection-induced hypoxia injury may trigger pulmonary vasoconstriction and pulmonary hypertension, leading to cardiac insufficiency and heart failure [92,93]. Furthermore, hypoxia injury is likely to lead to secondary myocardial injury, thereby aggravating the impairment of cardiac function. Therefore, hypoxia injury may be an important mechanism of cardiovascular injury caused by SARS-CoV-2 infection.

Psychological injury

It has been reported that patients with COVID-19 pneumonia have different degrees of psychological pain, such as depression, fear, stress, and anxiety, which may affect the development and prognosis of the disease [94–96]. These physical and psychological stress processes could stimulate sympathetic nerve activity and enhance the release of catecholamines, causing a variety of cardiovascular dysfunctions, such as myocardial injury, cardiomyopathy, hypertension, coronary artery vasoconstriction, arrhythmia, and increased microvascular resistance [97,98]. Therefore, psychological injury is also a non-negligible factor causing cardiovascular injury in patients with COVID-19.

Role of General Practitioners in the Prevention and Control of Cardiovascular Disease during the Outbreak of COVID-19

During the COVID-19 outbreak, general practitioners working in the community were both gatekeepers and health promoters [99]. General practitioners are engaged in three phases of response to cardiovascular disease prevention and control in the fight against the COVID-19 outbreak. In phase 1, general practitioners help block the transmission of SARS-CoV-2 by monitoring people at designated checkpoints. In phase 2, general practitioners help identify high-risk groups with cardiovascular disease, and these groups will be specifically labeled for cardiovascular disease in their personal health files. If these people have a SARS-CoV-2 infection, general practitioners could conduct the initial treatment and then transfer patients timely to the hospital. In phase 3, general practitioners help provide rehabilitation for critically ill patients. Also, they help provide psychological counseling and support to the community, to eliminate fears and panic. Thus, general practitioners play a unique and irreplaceable role in the prevention and control of cardiovascular disease during the COVID-19 epidemic.

Drug Therapy for Cardiovascular Complications in Patients with COVID-19

Antiviral therapy

Although there are currently no specific effective therapies for COVID-19, various antiviral drugs are under active investigation. Of note, some antiviral drugs have been screened potentially for the treatment of COVID-19. Remdesivir is a nucleoside analogue prodrug with the broad-spectrum antiviral activity that interrupts virus RNA replication. It has been reported that remdesivir potently inhibits SARS-CoV-2 replication *in vitro* at low micromolar concentrations [100]. The first confirmed COVID-19 case in the USA was treated with intravenous remdesivir when the patient's clinical condition was getting worse [101]. Similar to remdesivir, ribavirin and arbidol also prevent the replication of RNA viruses and have been reported to produce certain benefits in the treatment of COVID-19 pneumonia [102–104]. Chloroquine, a widely used antimalarial and autoimmune disease drug, has been demonstrated to have *in vitro* activity against SARS-CoV-2 [100]. Moreover, the therapeutic benefit of chloroquine for patients with COVID-19 was described in clinical studies [105]. Additionally, lopinavir/ritonavir, a protease inhibitor that can suppress the replication and synthesis of the HIV, was reported to improve the outcome of critically ill patients with SARS by alleviating ARDS [106]. It has been reported that lopinavir/ritonavir can successfully treat COVID-19, although the first randomized open-label trial showed that the benefits of lopinavir/ritonavir treatment do not go beyond standard care [107]. In this study, lopinavir/ritonavir resulted in a median time to clinical improvement that was 1 day shorter than the standard care group [107].

Antiviral drug-induced cardiotoxicity during the treatment of COVID-19 deserves attention. A rare but serious side effect of chloroquine therapy is cardiotoxicity. It has been reported that chloroquine in overdose (as in self-poisoning or when given by rapid intravenous administration) can cause hypotension, arrhythmias, and conduction disturbances [108–110]. In addition, the protease

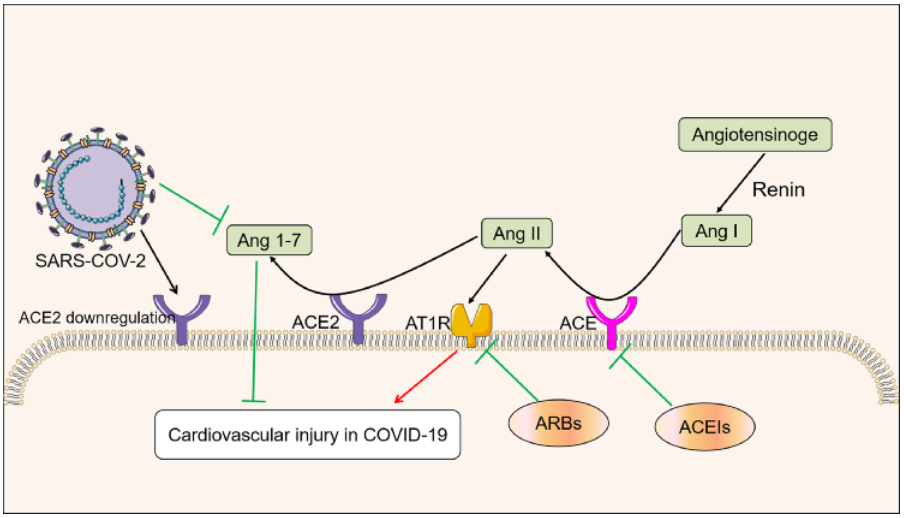

Figure 3. Schematic diagram of the role of the RAS in cardiovascular injury and proposed SARS-CoV-2 action Renin catalyzes angiotensinogen to generate Ang I. The production of Ang II from Ang I is enhanced by ACE, and Ang II induces cardiovascular injury by stimulation of the AT1R, while ACE2 negatively regulates this pathway and protects against cardiovascular injury. By contrast, SARS-CoV-2 infection is mediated by the binding of spike protein to ACE2 and downregulates the protective molecule ACE2, thereby resulting in cardiovascular injury. ACEIs and ARBs, as inhibitors of the RAS, can inhibit ACE and AT1R, respectively, thus reducing cardiovascular injury.

inhibitor lopinavir/ritonavir is also linked to increased risk of cardiovascular disease. It has been reported that lopinavir/ritonavir could cause hyperlipidemia and promote endothelial cell dysfunction [111–113], thereby increasing the risk of cardiovascular events. Therefore, it is necessary to closely monitor and manage the cardiotoxicity in patients undergoing antiviral therapy.

RAS inhibitors

ACE inhibitors (ACEIs) and Ang II receptor blockers (ARBs), as inhibitors of the RAS, are widely utilized in the treatment of cardiovascular diseases, such as hypertension, myocardial infarction, and heart failure. Importantly, the ACE2 receptor is the key entry point for SARS-CoV-2. There are concerns about the treatment with RAS inhibitors that may have the potential to upregulate ACE2 and increase the risk of developing a severe and fatal SARS-CoV-2 infection. However, ACEIs increase Ang I and decrease Ang II levels by inhibiting ACE, not ACE2 (Fig. 3). It has been reported that ACEIs in clinical use do not directly affect the activity of ACE2 [114]. Although ARBs have been shown to upregulate ACE2 in animal studies, this would not establish that it is sufficient to promote SARS-CoV-2 entry [115–117]. Moreover, Meng *et al.* [118] observed that COVID-19 patients with hypertension receiving ACEIs or ARBs therapy had a lower rate of severe diseases and a trend toward lower levels of CRP and IL-6 in peripheral blood. Meanwhile, ACEIs or ARBs therapy could significantly increase $CD3^+$ and $CD8^+$ T cell counts in peripheral blood and reduce the peak viral load [118], suggesting that RAS inhibitors could facilitate immune recovery of COVID-19 patients. Studies have revealed that patients with COVID-19 have increased Ang II levels compared to healthy people [77]. Therefore, these studies support the benefits of using ACEIs or ARBs to improve the clinical outcomes of patients with COVID-19 complicated by cardiovascular diseases. It is strongly recommended that COVID-19 patients who are taking ACEIs or ARBs for hypertension, heart failure, or other medical indications should not be discontinued.

Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody that effectively blocks IL-6R-mediated signal transduction. IL-6 is the key molecule of cytokine storm syndromes and its level is markedly elevated in patients with COVID-19 [29,119]. Thus, tocilizumab may be a promising therapeutic option for patients with COVID-19 by virtue of its ability to inhibit cytokine storm syndromes. A multicenter, randomized controlled trial of tocilizumab (IL-6 receptor blockade) has also been approved in patients with COVID-19 and elevated IL-6 in China (ChiCTR2000029765) [120]. In addition, it is noteworthy that tocilizumab therapy can decrease hepatic LDL receptor expression and increase serum LDL cholesterol, high-density lipoprotein cholesterol, and triglyceride levels [121], which may increase the risk of atherosclerotic cardiovascular disease. Thus, it is necessary to monitor the changes in lipid profile when tocilizumab is used for the treatment of COVID-19 patients with cardiovascular disease.

Statins

Statins are widely used for the secondary prevention of patients with coronary heart disease and have the effects of lowering lipids, anti-inflammation, and stabilizing plaque. Thus, statins can be used for the treatment and prevention of cardiovascular disease in patients with COVID-19. Notably, rhabdomyolysis was reported as an important side effect of statin therapy, and this risk is greater with concurrent use of drugs that suppress cytochrome p450-3A4 (CYP3A4), such as lopinavir and ritonavir [122]. Thus, statins should not be used together with lopinavir/ritonavir for patients with COVID-19.

Other treatments

Other treatments include antiplatelet therapy, diuretics, and calcium antagonists. Blood pressure and heart rate should be closely monitored when calcium antagonists are used in combination with other

antiviral drugs. In addition, some drugs, such as coenzyme Q, vitamin C, and creatine phosphate sodium, may be used for myocardial protection and myocardial nutrition in patients with COVID-19.

Conclusion

The COVID-19 pandemic has caused a large number of deaths with over 70,000,000 confirmed cases worldwide, posing a serious threat to public health. Cardiovascular disease is a common comorbidity in patients with COVID-19 and such patients are at higher risk of severe disease and mortality. SARS-CoV-2 triggers viral infection–related heart damage by multiple mechanisms, such as direct injury, downregulation of ACE2, immune injury, hypoxia injury, and psychological injury. Therefore, it is necessary to continue to monitor the cardiovascular complications of COVID-19 and identify the risk factors for poor prognosis (e.g. age, smoking, obesity, blood pressure, *etc*.). Moreover, general practitioners will play an important role in the prevention and control of cardiovascular disease during the outbreak of COVID-19. They also conduct daily health monitoring and provide counseling for the patients' psychological problems. Many COVID-19 patients complicated by cardiovascular disease are treated with ACEIs/ARBs, and clinical studies are necessary to explore the potential relationship between ACEIs/ARBs and COVID-19 prognosis. In addition, it is noteworthy that COVID-19 may become a chronic epidemic like seasonal influenza due to genetic recombination. Therefore, the design and development of vaccines and monoclonal antibodies against SARS-CoV-2 are also needed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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