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Review

COVID-19 and cardiovascular diseases

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The coronavirus disease 2019 (COVID-19) remains a global public health emergency. Despite being caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), besides the lung, this infectious disease also has severe implications in the cardiovascular system. In this review, we summarize diverse clinical complications of the heart and vascular system, as well as the relevant high mortality, in COVID-19 patients. Systemic inflammation and angiotensin-converting enzyme 2-involved signaling networking in SARS-CoV-2 infection and the cardiovascular system may contribute to the manifestations of cardiovascular diseases. Therefore, integration of clinical observations and experimental findings can promote our understanding of the underlying mechanisms, which would aid in identifying and treating cardiovascular injury in patients with COVID-19 appropriately.

Keywords: COVID-19, cardiovascular diseases, SARS-CoV-2, ACE2, systemic inflammation

Introduction

Since early December of 2019, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly transmitted around the world and posed an unprecedented public health threat to human beings (Hui et al., 2020; Lu et al., 2020a; Wang et al., 2020). As of September 6, 2020, there have been 26763217 confirmed cases of COVID-19, including 876616 deaths, reported to the World Health Organization (World Health Organization, 2020). COVID-19 pandemic, therefore, remains a public health emergency of international concern, which is anticipated to be a lengthy duration and requires long-term response measures.

After the outbreak, the pathogen of COVID-19 was soon identified to be a β-coronavirus, with sequences highly homologous to that of bat coronaviruses (CoVs) (Lu et al., 2020b; Wu et al., 2020; Zhou et al., 2020b). SARS-CoV-2 shows 79% sequence identity to SARS-CoV (Lu et al., 2020b; Zhou et al., 2020b) that led to the outbreak of the SARS epidemic in 2002–2003 (Drosten et al., 2003). Similar to SARS-CoV, spike protein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor of host cells for invasion (Du et al., 2009; Ge et al., 2013; Cui et al., 2019; Zhou et al., 2020b). Subsequently, the spike protein is cleaved by transmembrane protease serine 2 (TMPRSS2) of the host cell for priming, which facilitates the fusion of viral membrane with the host cell membrane (Hoffmann et al., 2020). Owing to the high expression of ACE2 in alveolar epithelial type II cells, the lung becomes a vulnerable organ for SARS-CoV and SARS-CoV-2 infection (Hamming et al., 2004; Zhang et al., 2020a). Like infection by other respiratory viruses, the symptoms of COVID-19 include fever, dry cough, dyspnea, myalgias, fatigue, and diarrhea, as well as imaging and laboratory abnormalities, such as bilateral ground-glass opacities on chest CT scans and lymphopenia (Huang et al., 2020; Wu and McGoogan, 2020). During its progression into severe cases, COVID-19 may be presented as pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and specific organ dysfunction (Murthy et al., 2020; Wang et al., 2020).

Cardiovascular manifestations are diverse in COVID-19 patients. For example, some patients showed cardiovascular system symptoms such as palpitation and chest distress as their first symptoms (Zheng et al., 2020). Meanwhile, clinical data suggest that the susceptibility to SARS-CoV-2 infection and outcomes of COVID-19 are closely associated with pre-existing cardiovascular diseases (CVD) (Chen et al., 2020b;

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Wang et al., 2020). ACE2 is a component of the renin–angiotensin–aldosterone system (RAAS), which plays a critical role in the regulation of cardiovascular system homeostasis (Romero et al., 2015). The involvement of the cardiovascular system in COVID-19 has drawn attention to the potential bidirectional cause–effect relationship between SARS-CoV-2 infection and the impairment of the cardiovascular system. Given the presence of a large number of patients with CVD and the significance of the cardiovascular system, figuring out the interaction between SARS-CoV-2 infection and the cardiovascular system not only has evident implications for the diagnosis, treatment, and prognosis of COVID-19 but also is beneficial to the management of CVD patients in the context of lengthy pandemic.

Cardiovascular manifestations in COVID-19

Previous clinical studies have implied that COVID-19 leads to diverse cardiovascular complications (Chen et al., 2020b; Guan et al., 2020b; Huang et al., 2020; Shi et al., 2020b; Wang et al., 2020; Zhou et al., 2020a; Table 1). The potential cardiovascular complications in COVID-19 patients are described as follows (Figure 1).

Myocardial injury

According to the clinical case series, the incidence of myocardial injury (MI) ranges from 7.2% to 19.7% in COVID-19 patients (Chen et al., 2020b; Guan et al., 2020b; Huang et al., 2020; Shi et al., 2020b; Wang et al., 2020; Zhou et al., 2020a). MI is diagnosed with elevated serum levels of cardiac biomarkers or abnormalities of electrocardiography and echocardiography. Several lines of evidence have shown that MI is an independent risk factor for adverse outcomes, such as 11-fold increase in mortality (Shi et al., 2020b). Likewise, MI biomarkers, such as initial cardiac troponin I (cTnI), can predict the risk of in-hospital mortality among patients with severe COVID-19 (Shi et al., 2020a). Based on the biomarkers, MI in COVID-19 patients can be ascribed to two patterns. One of the patterns reflects cytokine storm, which is characterized by increased high-sensitivity cTnI tracking with other inflammatory biomarkers such as D-dimer and interleukin-6 (IL-6). Another pattern presents with predominantly cardiac symptoms indicating viral myocarditis or stress cardiomyopathy (Clerkin et al., 2020).

As mentioned above, the incidence of cardiac injury is relatively high in COVID-19 patients and positively related to mortality. Therefore, clinicians should pay attention not only to the symptoms of the respiratory system but also the symptoms, laboratory results, and auxiliary test of cardiac injury (Ruan et al., 2020).

Arrhythmias

Among the confirmed COVID-19 cases, the first visit of some patients to see a doctor is due to heart palpitations instead of fever or cough (Zheng et al., 2020). In a cohort study, heart palpitations were present in 7.3% of patients (Liu et al., 2020). As a case series revealed, the incidence of cardiac arrhythmia was 16.7% and cardiac arrhythmia was more prevalent in ICU COVID-19 patients (Wang et al., 2020). In addition, elevated levels of troponin T were likely to indicate potential development of malignant arrhythmias (ventricular tachycardia and fibrillation) in COVID-19 patients. Although mechanisms underlying the impact of COVID-19 on cardiac arrhythmias remain unclear, arrhythmia in COVID-19 patients might be caused by MI, cardiogenic shock, hypoxia, acid-base imbalance, and electrolyte disturbance (Lakkireddy et al., 2020).

Heart failure

Heart failure is also a common complication of COVID-19. A cohort study shows that the incidence of heart failure is 23% in all 191 patients and 49% in non-survived patients (Zhou et al., 2020a). Another study also supports the prevalence of heart failure as COVID-19-related complications and elevated levels of amino-terminal pro-B-type natriuretic peptide in almost half of the patients (Chen et al., 2020c). However, the causes of heart failure in COVID-19 patients remain unclear. Reduced diastolic function, pre-existing CVD comorbidities, acute MI triggered by COVID-19, and sepsis-associated cardiac dysfunction are all possible contributors to the etiology of heart failure in COVID-19 (Prabhu, 2004; Dewey et al., 2020; Fried et al., 2020; Mehra and Ruschitzka, 2020).

Coagulation abnormalities

Early studies have shown that vascular dysfunction might lead to cardiovascular complications of COVID-19 (Varga et al., 2020). Disseminated intravascular coagulation (DIC) and

Table 1 Prevalence of cardiovascular complications in COVID-19 patients.

Total cases	Severe cases[a]	MI		Arrythmia		Heart failure		Shock		Reference
		Among all patients	Among severe patients	Among all patients	Among severe patients	Among all patients	Among severe patients	Among all patients	Among severe patients	
138	36	7.2%	22.2%	16.7%	44.4%			8.7%	30.6%	Wang et al. (2020)
41	13	12%	31%					7%	23%	Huang et al. (2020)
99	23							4%		Chen et al. (2020b)
191	54	17%	59%			23%	52%	20%	70%	Zhou et al. (2020a)
1099	173							1.1%	6.4%	Guan et al. (2020b)
416		19.7%	73.7%							Shi et al. (2020b)

[a]Severe cases: patients in ICU/with ventilation/dead.

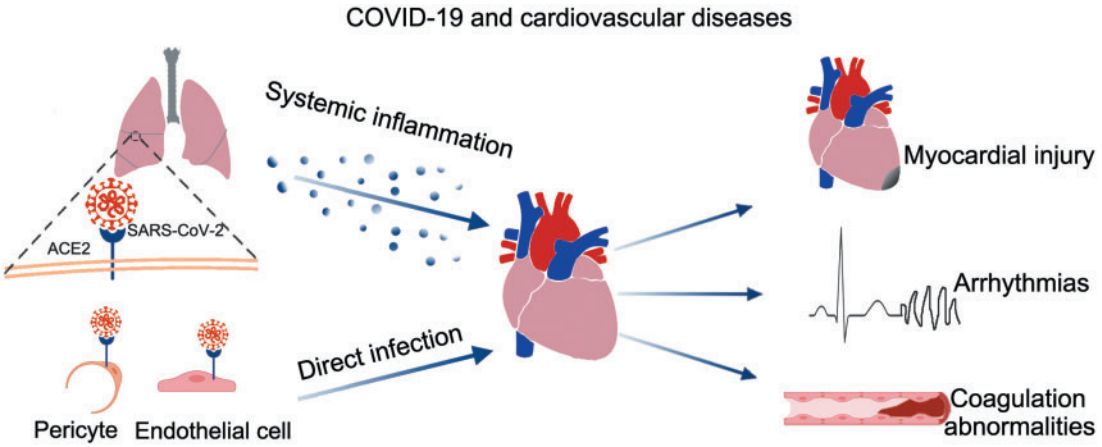

Figure 1 Schematic model of COVID-19 and CVD.

thromboembolic events, in which the impairment of endothelium plays a key role, are highly prevalent in COVID-19 patients and numerous studies have indicated that abnormal coagulation parameters are strongly associated with adverse outcomes in COVID-19 patients (Guan et al., 2020b; Tang et al., 2020; Zhou et al., 2020a). DIC caused by COVID-19 is presented as elevated D-dimer and fibrin/fibrinogen-degradation products but slightly prolonged prothrombin time, partial thromboplastin time, as well as modestly thrombocytopenia (Arachchillage and Laffan, 2020; Connors and Levy, 2020). Consistent with these laboratory findings, autopsy studies and case reports both show deep vein thrombosis and pulmonary embolism in COVID-19 patients (Danzi et al., 2020; Wichmann et al., 2020; Zhang et al., 2020b).

Cardiovascular complications in children: hyperinflammatory syndrome

It is reported that the hospital mortality is much less among patients younger than 40 years compared to patients aged 80–89 years (5% vs. 60%; Wiersinga et al., 2020). Accordingly, the confirmed COVID-19 cases were less frequently found in children with no or mild symptoms (CDC COVID-19 Response Team, 2020; Dong et al., 2020), but the number of children infected has increased steadily with the increased risk of cardiovascular impairment in child patients (Kim et al., 2020; Sanna et al., 2020). Findings from several countries uncovered a new phenomenon, i.e. previously asymptomatic children with SARS-CoV-2 infection can suffer from hyperinflammatory syndrome with multiorgan involvement (Riphagen et al., 2020; Verdoni et al., 2020). Although the underlying mechanism is still unclear, the proinflammatory effect of SARS-CoV-2 infection is likely responsible for cardiovascular symptoms in children.

High mortality in COVID-19 patients with pre-existing CVD

At the very beginning of the epidemic, clinical data displayed a prevalence of CVD in confirmed cases, such as hypertension, diabetes, and other CVD. These indicate that pre-existing CVD may predispose the patients to SARS-CoV-2 infection (Guan et al., 2020a, b; Huang et al., 2020; Ruan et al., 2020; Wang et al., 2020; Zhou et al., 2020a). Similarly, in countries besides China, case series also demonstrate the prevalence of CVD in COVID-19 patients (Goyal et al., 2020; Grasselli et al., 2020; Richardson et al., 2020). Moreover, the prevalence of pre-existing diseases, especially CVD, was much higher in severe cases and deaths of COVID-19, indicating that pre-existing CVD could predict adverse outcomes in SARS-CoV-2 infection (Guan et al., 2020a; Ruan et al., 2020). In addition, pre-existing CVD might also render the patients to be more susceptible to SARS-CoV-2-induced MI (Shi et al., 2020b). Therefore, it is speculated that SARS-CoV-2 infection superimposed on pre-existing CVD may exacerbate the injury already present in the cardiovascular system (Shi et al., 2020b). It is thus sensible to suggest that patients with pre-existing CVD should be triaged and treated with priority.

Nevertheless, it remains unsure whether patients with underlying CVD are more likely to acquire the infection and develop into severe COVID-19 (Cappuccio and Siani, 2020), as most of the case series reported have bias such as age and presence of multi-comorbidities (Cappuccio and Siani, 2020). In addition, some scientists postulate that the enhanced expression of ACE2 in CVD patients may provide convenient portals for SARS-CoV-2 infection (Zheng et al., 2020). However, attenuated expression of ACE2 is reported in patients with heart failure, diabetes, and hypertension (Chen et al., 2020a; Hafiane, 2020).

Mechanisms underlying the interaction between cardiovascular impairment and SARS-CoV-2 infection

Cardiovascular injury caused by systemic inflammation

Systemic inflammation seems to be the most prominent mechanism underlying cardiovascular complications of COVID-19. After the infection of SARS-CoV-2, the virus–host interactions cause an innate immune response and activate pattern recognition receptors (PRRs), which will trigger the secretion of the antiviral cytokine

INF-γ and pro-inflammatory cytokines including IL-1, IL-6, and tumor necrosis factor-α (TNF-α) (Vabret et al., 2020).

IL-1, for example, is reported to play important roles in CVD (Buckley and Abbate, 2018). IL-1 suppresses β-adrenergic receptor signaling, which is caused by incorrect cytoplasmic calcium handling and leads to impaired cardiac contraction with subsequent heart failure (Van Tassell et al., 2013). IL-1 also induces nitric oxide production to lower myocardial contractility through inhibition of anaerobic glycolysis in cardiac myocytes (Tatsumi et al., 2000). In addition, IL-6 is a surrogate for IL-1 activity, whose circulating levels are positively associated with heart failure events and death (Deswal et al., 2001). IL-6 binds to the soluble IL-6 receptor (IL-6R) and initiates subsequent signaling through engagement with 130-kDa glycoprotein (Rose-John and Heinrich, 1994). Excessive synthesis of IL-6 (Kang et al., 2019) and activation of trans-signaling pathway of IL-6 are deleterious for the cardiovascular system. For instance, increased IL-6 levels inhibit NO–cGMP-mediated relaxation pathway in blood vessels of pregnant rats (Orshal and Khalil, 2004). IL-1 also induces the expression of TNF-α (Warner and Libby, 1989). Transgenic mice with cardiac-specific overexpression of TNF-α display dilated cardiomyopathy, possibly due to electrical remodeling (Kubota et al., 1997; Petkova-Kirova et al., 2006). High concentrations of TNF-α could impair Keap1/Nrf2 response and result in cardiomyocyte death because of the severe oxidative stress, while low levels seem to be protective (Shanmugam et al., 2016).

However, coronaviruses can escape from the innate immunity by blocking IFN signaling and lead to an imbalance between antiviral and proinflammatory responses (Vabret et al., 2020). Meanwhile, the viral replication in host airway epithelial cells can cause pyroptosis and trigger the subsequent inflammatory response (Yap et al., 2020). In severe cases, the pro-inflammatory process cannot be contained and thus leads to the badly damaged lung in addition to the direct damages caused by viral infection, manifested as ARDS (Xu et al., 2020). The overloaded inflammatory factors may also enter circulation and cause cytokine storm as well as multi-organ damages in COVID-19 patients (Hendren et al., 2020), with the involvement of the cardiovascular system.

Accordingly, clinical studies are focusing on reagents that can attenuate IL-1, IL-6, and TNF-α signaling for anti-inflammatory treatment of CVD (Ridker and Lüscher, 2014; Zhu et al., 2018), which may be potentially useful in COVID-19 treatment. The impact of tocilizumab, an IL-6R blocker, is currently being tested in a clinical trial (http://www.chictr.org.cn/showprojen.aspx? proj=49409; Gul et al., 2020).

The cardiovascular system is a potential direct target of SARS-CoV-2

ACE2 is thought to be responsible for the manifestations of the cardiovascular system in COVID-19. On the one hand, as the host receptor for SARS-CoV-2 infection, the distribution of ACE2 partly determines tissue tropism of this new type of virus. Nonetheless, besides the lung, ACE2 is also expressed in the kidney, heart, enterocytes of the small intestine, and vascular endothelial cells, which may partially explain the extrapulmonary manifestation of SARS-CoV and SARS-CoV-2 infection (Crackower et al., 2002; Tikellis et al., 2003; Hamming et al., 2004; Chen et al., 2020a). On the other hand, as a functional enzymatic component of RAAS, ACE2 and ACE (homologous protein of ACE2) participate in the maintenance of cardiovascular homeostasis, regulation of blood pressure, electrolyte balance, as well as the function of organs (Romero et al., 2015). Angiotensinogen, which is mainly produced in the liver, is cleaved by rennin to angiotensin I, which is then degraded into Ang II by ACE (Lindpaintner et al., 1990; Voors et al., 1998; Hamming et al., 2007). Ang II is the major effector molecule in the RAAS. Acting on angiotensin type 1 receptor (AT1R), Ang II can promote vasoconstriction, sodium retention, oxidative stress, inflammation, and fibrosis (South et al., 2020). Ang II is upregulated in many cardiovascular and renal diseases (Hamming et al., 2007). In contrast, ACE2 degrades Ang II and generates Ang(1–7), which antagonizes the effect of Ang II via the Mas receptor to promote vasodilation, hypotension, and apoptosis (Hamming et al., 2007).

Clinical evidence shows viral inclusion structures in endothelial cells of multi-organs and diffuses endothelial inflammation in COVID-19 patients, which could lead to vascular dysfunction and vasoconstriction with subsequent organ ischemia as well as coagulation abnormalities (Romero et al., 2015). Expression of ACE2 in cardiomyocytes and pericytes may also make the heart a direct target of SARS-CoV-2 invasion (Chen et al., 2020a). Endomyocardial biopsy shows low-grade myocardial inflammation and viral particles in interstitial cells of the heart (Tavazzi et al., 2020). An autopsy has also indicated the presence of mild lymphocytic myocarditis and viral RNA in the hearts of patients with COVID-19 (Schaller et al., 2020; Wichmann et al., 2020). Nevertheless, the question of whether SARS-CoV-2 can directly proliferate in cardiomyocytes has not been solved (Hafiane, 2020).

Previous studies indicated that infection of SARS-CoV could lead to the decreased expression of ACE2 and in turn aggravate the lung injury, suggesting a lung-protective function of ACE2 (Imai et al., 2005; Kuba et al., 2005). Although the exact mechanism underlying ACE2-protective effects on lung injury remains unknown, it has been reported that ACE2 may prevent lipopolysaccharide-induced ARDS by inhibiting MAPKs and NF-κB signaling pathway (Li et al., 2016). Besides lung-protective function, ACE2 also shows cardioprotective effects (Crackower et al., 2002; Keidar et al., 2007; South et al., 2020). A previous study shows that the expression of ACE2 is markedly reduced in hypertensive rat strains and loss of ACE2 in mice leads to severe cardiac dysfunction (Crackower et al., 2002). Similar to SARS-CoV, infection of SARS-CoV-2 is likely to result in the loss of ACE2, which would be predicted to exacerbate cardiovascular symptoms in patients with underlying CVD (South et al., 2020). Because of the imbalance of the renin–Ang system mediated by ACE2 depletion, it is speculated that COVID-19 hastily involves the cardiovascular

system (Hafiane, 2020). Therefore, it seems that infusion of recombinant human ACE2 to neutralize SARS-CoV-2 might be a promising therapy approach (Monteil et al., 2020; Zhang et al., 2020c). The relevant clinical trial was proposed but subsequently withdrawn (https://clinicaltrials.gov/ct2/show/NCT04287686; South et al., 2020).

ACE inhibitors and angiotensin receptor blockers (ARBs) are commonly used medications for hypertension and other CVD (Ferrario et al., 2005; Soler et al., 2008). Their reported effect on increasing ACE2 expression in animal models (Ferrario et al., 2005) made physicians consider whether these drugs should be discontinued to reduce the possibility of SARS-CoV-2 infection. Medical societies around the world have reached an agreement that RAAS antagonists for those patients who are currently prescribed with these agents are recommended to continue (Bozkurt et al., 2020; ESC Council on Hypertension, March 13, 2020; Han et al., 2020), as these drugs neither increase susceptibility to SARS-CoV-2 infection nor increase the risk of adverse outcomes of COVID-19 (Mancia et al., 2020; Mehta et al., 2020; Reynolds et al., 2020).

Potential molecular mechanisms of COVID-19 pathogenesis in the cardiovascular system: on the basis of other coronavirus infections

Ang II–AT1R axis activates mitogen-activated protein kinases (MAPK) (Muslin, 2008), while Ang(1–7) represses MAPK signaling (Zhang et al., 2014). Meanwhile, CVD are associated with RAAS activation and ACE2 downregulation (Nehme and Zibara, 2017), indicating an activation of the MAPK signaling pathway. Previous studies with other types of coronaviruses show that SARS-CoV spike protein could trigger ERK1/2 phosphorylation and subsequently lead to increased cyclooxygenase-2 expression and IL-8 release (Chang et al., 2004; Mizutani et al., 2004a; Liu et al., 2007). In addition, inhibition of the MAPK pathway is shown to suppress coronavirus replication (Cai et al., 2007). Another MAPK, c-Jun N-terminal kinase (JNK), is also phosphorylated with upregulated expression after SARS-CoV infection, thus resulting in apoptosis of the infected cells (Mizutani et al., 2004a; Surjit et al., 2004). Moreover, infection of SARS-CoV could also activate p38 MAPK and induce apoptotic cell death (Mizutani et al., 2004b). Accordingly, as a new type of coronavirus, SARS-CoV-2 pathogenesis also leads to increased severity in patients with pre-existing CVD, which may be partially attributed to the activated MAPK signaling.

Perspectives

The COVID-19 epidemic has changed our lives in an unprecedented way and remains unpredictable within the near future. Even with novel platforms and strategies, SARS-CoV-2 vaccine development would take 12–18 months (Lurie et al., 2020) and is unavailable at present. Accordingly, there is no effective intervention currently other than supportive care. Regular epidemic prevention and control measures, such as social distancing and wearing masks, are required to avoid overshooting critical care capacities. A prolonged or intermittent social distancing may continue to 2022 (Kissler et al., 2020). Facing the COVID-19 pandemic, it is of great significance for cardiovascular communities to provide timely and effective treatment for COVID-19 patients as well as continuous care to uninfected patients with pre-existing CVD (Driggin et al., 2020), due to the interaction of SARS-CoV-2 infection and the cardiovascular system. Additional studies on the cellular and molecular mechanisms underlying COVID-19 and CVD are undoubtedly warranted.

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