Interaction between Cardiovascular Diseases and COVID-19.

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Abstract

Clinical studies have reported an association between COVID-19 and cardiovascular disease. Pre-existing disorder seems to be linked with worse outcomes and increased risk of death in patients with COVID-19, whereas COVID-19 itself also can induce myocardial injury, arrhythmia, acute coronary syndrome and venous thromboembolism. Potential drug-disease interactions affecting patients with COVID-19 and comorbid cardiovascular diseases also are becoming a significant concern. In this Review, we summarize the present understanding of COVID-19 entering in to the host cell from basic mechanisms to clinical perspectives, that specialize in the interaction between COVID-19 and therefore the circulatory and respiratory system.

Keywords: COVID-19, Cardiovascular disease, Myocardial injury, Myocarditis, Acute coronary syndrome.

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Introduction

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a member of the genus Betacoronavirus like the two other coronaviruses that have caused pandemic diseases (severe acute respiratory syndrome coronavirus (SARS-CoV)) and Middle East respiratory syndrome coronavirus (MERS-CoV) [1-3]. As with SARS-CoV and MERS-CoV, SARS-CoV-2 causes a respiratory infection, which leads to viral pneumonia and Acute Respiratory Distress Syndrome (ARDS) in some patients. However, in addition to respiratory symptoms, uncontrolled SARS-CoV-2 infection can trigger a cytokine storm, whereby pro-inflammatory cytokines and chemokines such as tumour necrosis factor-α, IL-1β and IL-6 are overproduced by the immune system, resulting in multiorgan damage. Furthermore, COVID-19 causes coagulation abnormalities in a substantial proportion of patients, which can lead to thromboembolic events.

COVID-19 seems to promote the development of cardiovascular disorders, such as myocardial injury, arrhythmias, Acute Coronary Syndrome (ACS) and venous thromboembolism [4-6]. Children with COVID-19 have also been reported to develop hyper-inflammatory shock with features akin to Kawasaki disease, including cardiac dysfunction and coronary vessel abnormalities [7]. Together, these data indicate the presence of a bidirectional interaction between COVID-19 and the cardiovascular system, but the mechanisms underlying this interaction remain elusive. The high burden of systemic inflammation associated with COVID-19 has been proposed to accelerate the development of subclinical disorders or cause de novo cardiovascular damage [8,9-11]. ACE2, which is a key surface protein for virus entry and part of the Rennin-Angiotensin-Aldosterone System (RAAS), is also thought to be involved in this interaction on the basis of findings from animal models [9-12]. The fast-moving nature of this research field necessitates the integration of available biological data with clinical findings of COVID-19 to improve our understanding of the pathophysiology of the disease and to contribute to the development of potential therapies.

The Cardiovascular System and COVID-19

The process of SARS-CoV-2 entering host cells in the lungs and attacking other organs: Briefly, the receptor-binding domain of the spike glycoprotein binds to the tip of subdomain I of ACE2 [11]. Membrane fusion of the virus and the host cell is activated after binding, and viral RNA is subsequently released into the cytoplasm, establishing infection. For SARS-CoV infection, intact ACE2 or its transmembrane domain is internalized together with the virus [12]. The catalytically active site of ACE2 is not occluded by the spike glycoprotein, and the binding process is independent of the peptidase activity of ACE2. Some transmembrane proteinases (such as a Disinterring and Metallopeptidase Domain 17 (ADAM17), Transmembrane Protease Serine-2 (TMPRSS2), and TNF-converting enzyme and proteins (such as vimentin and clathrin) may be involved in the binding and membrane fusion processes. For example, ADAM17 can cleave ACE2 to cause ectodomain shedding, and TMPRSS2 can cleave ACE2 to market viral uptake.

ACE2 is expressed in nearly all human organs in varying degrees. In the respiratory system, the traditional immune-histochemical method and recently introduced single-cell RNA-sequence analysis revealed that ACE2 is mainly expressed on type II alveolar epithelial cells, but weakly expressed on the surface of epithelial cells in the oral and nasal mucosa and nasopharynx, indicating that the lungs are the primary target of SARS-CoV-2. Moreover, ACE2 is highly expressed on myocardial cells, proximal tubule cells of the kidney, and bladder urothelial cells, and is abundantly expressed on the enterocytes of the small intestine, especially in the ileum. The cell-free and macrophage phagocytosis-associated virus may spread from the lungs to other organs with high ACE2 expression through blood circulation (Figure 1). For example, up to 67% of patients who developed diarrhea during the course of SARS and quite a

number of patients with COVID-19 showed enteric symptoms. Active viral replication in enterocytes of the small intestine has been reported, and SARS-CoV-2 has been successfully isolated from fecal specimens.

Underlying cardiovascular comorbidities: Cardiovascular Disease (CVD) is a common comorbidity observed in patients infected with SARS or MERS (with a prevalence of 10% and 30%, respectively) [13,14]. A series of reports on the clinical characteristics of patients with COVID-19 have also described similar findings. Early reports from China found that CVD and its risk factors, such as hypertension and diabetes mellitus, were common pre-existing conditions in patients with COVID-19, but the definition of CVD used in each study was vague [15,16]. In an early report from Wuhan involving 41 patients who were hospitalized with COVID-19 by 2 January 2020, the prevalence of any comorbidity was 32% and the most common underlying diseases were diabetes (20%), hypertension (15%) and other CVDs (15%) [15]. The high prevalence of these comorbidities was confirmed in subsequent studies. Importantly, the prevalence of these pre-existing conditions was higher in critically ill patients (such as those admitted to the Intensive Care Unit (ICU)) and in those who died. In a single-centre cohort study of 138 patients hospitalized with COVID-19 in Wuhan, 46% of patients had any comorbidity (72% of patients in the ICU), 31% of patients had hypertension (58% of patients in the ICU), 15% of patients had other CVDs (25% of patients in the ICU) and 10% of patients had diabetes (22% of patients in the ICU) [17]. Similarly, in a multi-centre cohort study involving 191 patients hospitalized with COVID-19 in Wuhan, 48% of patients had any comorbidity (67% of those who died), 30% of patients had hypertension (48% of those who died), 19% of patients had diabetes (31% of those who died) and 8% of patients had coronary heart disease (24% of those who died). Furthermore, in a report involving 1,099 patients with COVID-19 from mainland China, 24% of patients had any comorbidity (39% of critically ill patients), 15% of patients had hypertension (24% of critically ill patients), 7% of patients had diabetes (16% of critically ill patients) and 3% of patients had coronary heart disease (6% of critically ill patients). The overall case fatality rate of COVID-19 reported by the Chinese Center for Disease Control and Prevention as of 11 February 2020 was 2.3% (1,023 deaths among 44,672 confirmed cases). The individual case fatality rate of patients with CVD was 10.5% (highest among those with any comorbidities, including chronic respiratory disease (6.3%) or cancer (5.6%), the case fatality rate of patients with diabetes was 7.3% and that of patients with hypertension was 6.0%. Of note, these early approximations of case fatality rate are likely to be overestimated given that the estimates did not account for the many people who had the virus but were not tested.

A similar trend in the prevalence of comorbidities has been reported by researchers in other countries. In a report involving 1,591 patients with COVID-19 who were admitted to the ICU in Italy, 49% of patients had pre-existing hypertension, 21% had CVD and 17% had diabetes 46. Furthermore, in a report of 393 consecutive patients hospitalized with COVID-19 in New York, USA, up to 50% of patients had hypertension (54% of ventilated patients), 36% had obesity (43% of ventilated patients), 25% of patients had diabetes (28% of ventilated patients) and 14% of patients had coronary artery disease (19% of ventilated patients). Of note, this study from New York highlighted the high prevalence of comorbid obesity among patients with COVID-19, which had not been reported in the studies on patients in China probably owing to differences in the background prevalence of obesity between the USA and China. Investigators in this study suggest that obesity might also be a risk factor for respiratory failure and the need for invasive mechanical ventilation.

Diverse cardiovascular manifestations: Although the predominant clinical manifestation of COVID-19 is viral pneumonia COVID-19 can also cause cardiovascular disorders such as myocardial injury, arrhythmias, ACS and thromboembolism Figure 1. Some patients who present without the typical symptoms of fever or cough have cardiac symptoms as the first clinical manifestation of COVID 19. Myocardial injury during the course of COVID-19 is independently associated with high mortality.

Furthermore, a possible link between COVID-19 and a Kawasaki disease-like syndrome has been described in children.

Myocardial injury and myocarditis: Acute myocardial injury, as evidenced by elevated levels of cardiac biomarkers or electrocardiogram abnormalities, was observed in 7%-20% of patients with COVID-19 in early studies in China. Furthermore, a subsequent study demonstrated that markers of myocardial injury were predictive of the risk of in hospital mortality in patients with severe COVID-19. The area under the receiver operating characteristic curve of the initial cardiac troponin I level for predicting in-hospital mortality was as high as 0.92. Other predictors of myocardial injury include advanced age, presence of comorbidities and high levels of C-reactive protein. Whether typical clinical features of myocarditis were present in patients who had elevated levels of cardiac troponins during the course of COVID-19 is unclear because most of the early studies did not include echocardiography or MRI data. Our understanding of the pathophysiology underlying SARS might help to determine whether SARS-CoV-2 can infect cardiac cells directly, given that SARS-CoV and SARS-CoV-2 share the same mechanisms of entry into the host cell and that the heart expresses high levels of ACE2.

Acute coronary syndrome: As with other infectious diseases, including SARS and influenza, COVID-19 can trigger ACS. The mechanisms underlying COVID-19 induced ACS might involve plaque rupture, coronary spasm or microthrombi owing to systemic inflammation or cytokine storm. For example, activated macrophages secrete collagenases that degrade collagen, a major constituent of the fibrous cap on atherosclerotic plaques, which can lead to plaque rupture. Activated macrophages are also known to secrete tissue factor, a potent pro-coagulant that triggers thrombus formation when the plaque ruptures. Direct endothelial or vascular injury caused by SARSCoV-2 infection might also increase the risk of thrombus formation and ACS.

Cardiovascular effects of antiviral drugs: At present, many research teams worldwide are focused on the development of drugs for the prevention and treatment of COVID-19. Of note, the development and testing of new drugs are time-consuming processes and not a viable strategy during this COVID-19 pandemic. Drug repurposing, in which existing medications

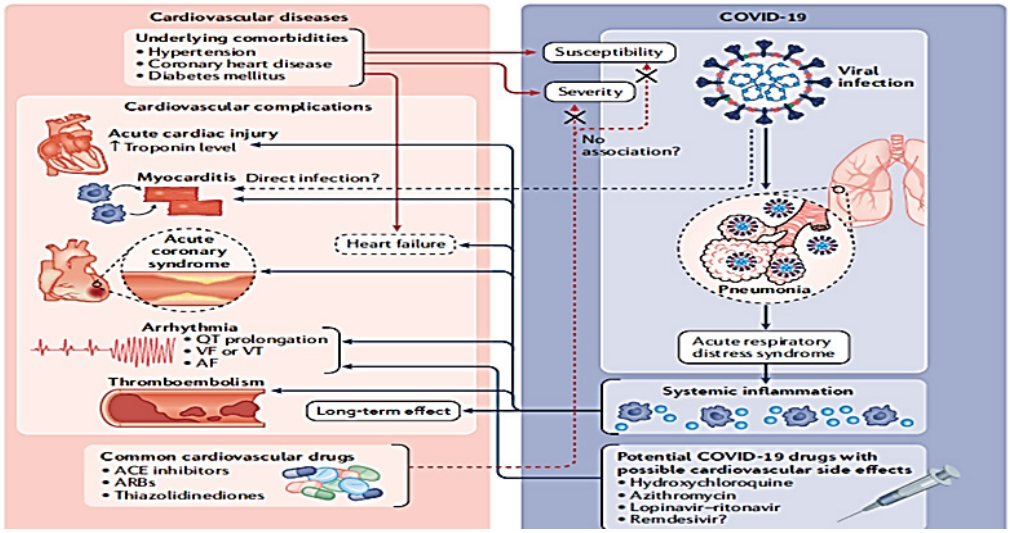

Figure 1: *Bidirectional interaction between cardiovascular diseases and COVID-19. AF: Atrial Fibrillation; VF: Ventricular Fibrillation; VT: Ventricular Tachycardia.*

that have already been approved for a disease are tested for a new condition, is currently the main approach in the search for new drugs for COVID-19. However, some of the drugs under investigation have known or unknown cardiovascular adverse effects or might be involved in drug-drug or drug-disease interactions.

Discussion

Cardiovascular comorbidities such as hypertension and coronary artery disease are associated with high mortality in patients with Coronavirus Disease 2019 (COVID-19). Drugs used to reduce cardiovascular risk such as Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) have numerous effects that might influence susceptibility to or the severity of COVID-19. Furthermore, although the main presentation of COVID-19 is viral pneumonia, COVID-19 can also induce cardiovascular manifestations including myocardial injury, myocarditis, arrhythmias, acute coronary syndrome and thromboembolism. Among these cardiovascular manifestations, myocardial injury has been independently associated with high mortality among patients with COVID-19. Finally, medications that have been proposed as treatments for COVID-19 such as hydroxychloroquine and azithromycin have proarrhythmic effects.

Conclusion

Mechanistically, the interaction between the S protein and ACE2 is likely to have a central role in disease pathogenesis, especially in cardiovascular manifestations of this disease, and this interaction is a potential target for the prevention and treatment of COVID-19. Several hurdles need to be overcome in the study of the mechanisms underlying COVID-19. First, biological experiments using SARS-CoV-2 can be performed only in laboratories with a biosafety level 3 rating. Second, the use of animal models to mimic the disease process is associated with numerous challenges. The COVID-19 pandemic is changing our lives in unprecedented ways. Given the lack of safe and effective vaccines or proven treatments for COVID-19, our main strategy to combat the pandemic is social distancing.

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