Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Coronavirus Disease-2019 (COVID-19) and Cardiovascular Complications

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The coronavirus disease-2019 (COVID-19) has become a global pandemic. It has spread to more than 100 countries, and more than 1 million cases have been confirmed. Although coronavirus causes severe respiratory infections in humans, accumulating data have demonstrated cardiac complications and poor outcome in patients with COVID-19. A large percent of patients have underlying cardiovascular disease, and they are at a high risk of developing cardiac complications. The basics of the virus, the clinical manifestations, and the possible mechanisms of cardiac complications in patients with COVID-19 are reviewed. Before an effective vaccine or medicine is available, supportive therapy and identifying patients who are at high risk of cardiac complications are important.

Key Words: coronavirus disease-2019; cardiac complications; cardiac injury; inflammatory factors; pneumonia

SINCE the first case of the novel coronavirus (COVID-19) was first reported on December 31, 2019, in Wuhan, China, the rapid spread of the virus has led to a global pandemic. On March 11, the World Health Organization declared that the spread of COVID-19 had become a pandemic. On April 8, the cumulative numbers of diagnosed patients internationally were 1,514,866 with 88,444 cases of mortality.[1]

With accumulating data of COVID-19, cardiac complications have become a big concern. Myocardial injury also has been detected in COVID-19 patients and is confirmed to be associated with poor outcome.[2] The mortality rate among patients with underlying cardiovascular disease has been reported as 10.5%, which is much higher than that in the general population.[3] In addition, underlying cardiovascular diseases have been demonstrated as one of the risk factors for severe cases. Therefore, a systemic understanding of cardiac complications in COVID-19 patients is important. The aim of this review is to provide essential knowledge of COVID-19 infection, its clinical manifestations, and possible mechanisms of cardiac complications.

The Virus

The outbreak of COVID-19 started in early December 2019 when a series of pneumonia cases of unknown cause were detected in Wuhan, China.[4] On January 7, the pathogen was identified as a novel coronavirus by the Chinese Center for Disease Control and Prevention, and it was named 2019-nCoV by the World Health Organization on January 12, 2020, or SARS-CoV-2 by the International Committee on Taxonomy of Viruses. 2019-nCoV is made of a single-strand ribonucleic acid, and its genome has been confirmed to be closely related with the coronavirus SARS-CoV, that which causes severe acute respiratory syndrome (SARS).[5] Structural analysis has shown that 2019-nCoV has the ability to bind to the angiotensin-converting enzyme 2 receptors (ACE2) in humans. The presence of ACE2 protein in the lower respiratory tract and on the enterocytes in the small intestine suggests the possible entry of the virus,[6] and it has been confirmed that 2019-nCoV uses ACE2 to enter the host cell.[7]

Cardiovascular Disease and Cardiac Complications in COVID-19 Patients

Pneumonia and cardiac disease often present in the same patient. The association between pneumonia and cardiac

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complications has been confirmed previously.[8-10] New or worsening heart failure, arrhythmia, and myocardial infarction are common cardiac complications. Furthermore, 8% to 25.1% of patients with community-acquired pneumonia (CAP) develop at least 1 episode of cardiac complications during their hospital stay,[9,11,12] and patients with underlying cardiovascular disease are more likely to develop CAP.[13] In-hospital cardiac complications after pneumonia have been associated with mortality[9] and increased cardiovascular events on 2-year follow-up.[14]

Cardiac complications also have been reported in patients with coronavirus infections.[15-17] In SARS patients, hypotension and tachycardia are common but usually are self-limiting. Arrhythmia and cardiomegaly are rare in patients diagnosed with SARS.[15] Reversible subclinical diastolic dysfunction without systolic involvement also has been observed in SARS patients.[16] Acute myocarditis developed after infection of the Middle East respiratory syndrome coronavirus (MERS-CoV), and myocardial edema was confirmed with magnetic resonance imaging. Furthermore, severe left ventricular dysfunction was persistent on 3-month follow-up.[17]

The effects of COVID-19 on the cardiovascular system are both similar to and different from those of SARS and MERS. Among COVID-19 patients, cardiovascular disease is the most common comorbidity, and cardiac complications are the most common complications.[18,19]

The prevalence of hypertension and other cardiovascular disease has been reported as 15% to 32.6% and 2.5% to 15%, respectively.[2,18-21] Patients with underlying cardiovascular disease are more prone to develop cardiac injury,[2,22] be severely ill,[18] or require intensive care.[22]

Cardiac injury, which is indicated by elevated cardiac troponin I (cTnI), also has been confirmed in COVID-19 patients. The incidence of cardiac injury has ranged from 7.2% to 27.8%,[2,18,19,22,23] and its incidence in intensive care unit patients and deaths has been reported as 22.2% and 77%, respectively.[18,24] Patients with elevated cTnI levels have shown a higher rate of cardiovascular disease,[2] and cTnI was significantly increased in severely ill or deceased COVID-19 patients compared with patients with milder symptoms.[2,18,19,24,25] A higher cTnI level also was associated with greater complications[2] and mortality.[2,22] Elevated N-terminal pro-brain natiuretic peptide (NT-proBNP) level also has been demonstrated,[2] and patients with elevated cTnI levels were more likely to have elevated levels of NT-proBNP.[2] All these findings suggested the relationship between cardiac injury, cardiac dysfunction, and poor outcome. Monitoring cTnI longitudinally during hospitalization may help predict the progression of the disease.[25]

Left ventricular dysfunction, persistent hypotension, acute myopericarditis, myocarditis, arrhythmia, and heart failure also have been reported in COVID-19 patients.[18,26-29] Interstitial mononuclear inflammatory infiltration in heart tissue also provides evidence of myocarditis in COVID-19 patients.[30] However, in a recent report of case series from critically ill patients in the Seattle, WA, region, no cardiac dysfunction was detected on echocardiograms.[29] Both echocardiography and cardiac magnetic resonance imaging have been used widely in the evaluation of cardiac structural and functional changes, and the upcoming reports about their role in the diagnosis and prognostication of patients with COVID-19 are awaited.

Possible Mechanisms of Cardiac Complications

At present, the exact pathophysiological mechanisms of myocardial injury are not fully understood. Patient characteristics, the severity of infection, and host reaction all participate in the development of cardiac complications.[10] Direct damage by the virus, systemic inflammatory responses, instability of coronary plaque, and hypoxia have been proposed as possible mechanisms (Fig 1).[2]

Direct pathogen invasion in severe pneumonia patients has been confirmed. In patients with severe pneumococcal disease, Streptococcus pneumoniae was detected in the myocardium, leading to cardiac injury and local proinflammatory responses.[30] In addition SARS-CoV has been detected in 35% of patients with SARS, which suggests the possibility of direct damage to cardiomyocytes by the virus.[31] At present, there have been few reports about the

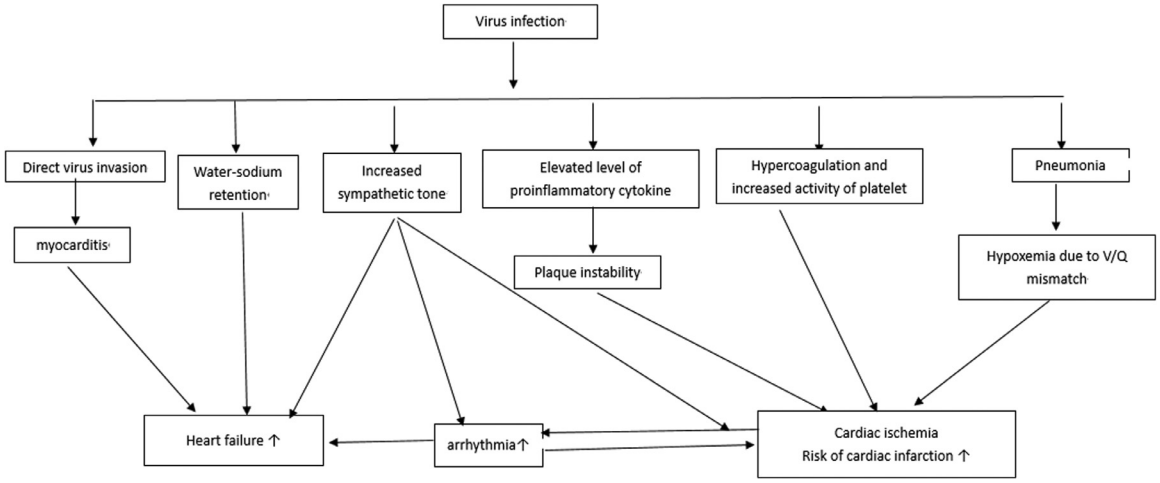

Fig 1. Possible mechanisms of cardiac complications in patients with coronavirus disease-2019. V/Q, ventilation/perfusion.

Table 1
Proinflammatory Cytokines and Their Role in Heart Disease

Cytokines	Role in Heart Disease	Selected Registered Trials for COVID-19
TNF-α	• Increased in patients with heart failure • Positive correlation between TNF-α expression and the severity of heart failure, left ventricular dilation/hypertrophy, and dysfunction	
IL-1β	• Elevated in patients with acute myocarditis	• NCT04330638
IL-6	• Increased in patients with acute myocardial infarction and heart failure • Predict the outcome of acute coronary syndrome and chronic heart failure	• NCT04321993 • NCT04317092 • NCT04330638 • NCT04329650
IL-8	• Increased in patients with acute myocardial infarction • Associated with mortality in acute coronary syndrome	
IL-10	• Elevated in patients with acute myocarditis • Poor outcome in Takotsubo cardiomyopathy	

Abbreviations: COVID-19, coronavirus 2019; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

pathologic features of COVID-19. Because SARS-CoV-2 is genetically closely related to SARS-CoV,[32] SARS-CoV-2 also may share the same mechanism with SARS-CoV.

Pneumonia is a highly proinflammatory disease,[28] and elevated levels of cytokines, which include C-reactive protein, interleukin-6 (IL-6), IL-8, IL-10, procalcitonin, IL-1β, and tumor necrosis factor-alpha (TNF-α), have been detected in COVID-19 patients, especially in intensive care unit patients.[19,33,34] Cytokines are important for infection control, but they also can lead to tissue damage and dysfunction (Table 1). The level of cTnI was positively associated with plasma high-sensitivity C-reactive protein,[2] which suggests the possible role of inflammatory storm in the development of cardiac injury. TNF-α has been detected in patients with heart failure,[35] and the positive correlation between TNF-α expression and the severity of heart failure, left ventricular dilation/hypertrophy, and dysfunction has been confirmed.[36-38] Increased levels of IL-1β have been found in patients with acute myocarditis,[30] and elevated concentrations of IL-6 were detected in patients with acute myocardial infarction and heart failure.[30] The level of IL-6 predicted the adverse cardiovascular events after acute coronary syndrome and chronic heart failure.[39,40] The serum IL-8 level is elevated in patients with acute myocardial infarction,[41] and it is associated with mortality in patients with acute coronary syndrome.[42] IL-10 is increased in patients with acute myocarditis,[43] and it is used to predict the poor outcome of Takotsubo cardiomyopathy.[44] The virus triggers a series of immune responses and the production of cytokines storm may contribute to systemic presentation and multiple organ dysfunctions in COVID-19 patients.

Instability of coronary atherosclerotic plaques,[45] increased coagulation activation[46] and platelet-aggregating activity,[47] and hypoxemia due to abnormal ventilation/perfusion lead to decreased myocardial oxygen supply and myocardial ischemia. Activation of the sympathetic nervous system leads to increased heart rate and peripheral resistance, which will further compromise coronary perfusion.[48]

Transient disturbance of endothelial function and vascular tone,[49,50] volume overload due to impaired sodium and water metabolism,[51] and cardiac arrhythmia[8] may contribute to decreased left ventricular function or worsening of heart failure.

Role of ACE2 in Cardiac Injury Induced by COVID-19

The role of ACE2 in cardiac injury induced by COVID-19 has been proposed.[22] SARS-CoV-2 shares the same host receptor (ACE2) with SARS-CoV, and its affinity to ACE2 is 10- to 20-fold greater than that of SARS-CoV.[52] The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) leads to increased expression of ACE2, and concerns about whether the use of ACEIs/ARBs will increase the risk of SARS-CoV-2 infection have been raised. However, in a mice model, SARS-CoV mediated myocardial injury through ACE2 with a remarkable decreased expression of ACE2,[31] and blocking the renin-angiotensin pathway can attenuate the severity of lung injury.[53] This result suggested the possible protective effect of ACEIs/ARBs in COVID-19 patients. Abrupt discontinuation of ACEIs/ARBs and switching to other antihypertensive drugs may result in adverse cardiac outcome. At present, clinical trials are recruiting patients to evaluate the safety and efficacy ACEIs/ARBs in COVID-19 patients. Guo et al.[2] demonstrated that there was no difference in mortality among patients with or without the use of ACEIs/ARBs. Before more data are available, the authors believe that it is unwise to discontinue ACEIs/ARBs in patients with COVID-19.[54]

Treatment of COVID-19

At present, there is no effective vaccination or drug for COVID-19; only sympathetic therapy and empirical/supportive treatment are available. COVID-19 patients have died due to their original comorbidities instead of pneumonia,[55] which suggested the necessity of special attention to their original comorbidities while treating pneumonia.

Whether the medications patients used for cardiovascular disease will interfere with the treatment or the outcome of COVID-19 is still unknown. The possible effects of these drugs on pneumonia were taken from studies on patients with CAP/other virus pneumonia. As previously mentioned, at present there is no evidence for stopping the administration of ACEIs/ARBs in COVID-19 patients. In addition, previous

reports about the effects of ACEIs/ARBs on outcome of patients with CAP have been conflicting.[56-58] Statins can reduce systemic inflammation[59] and improve outcome in CAP patients[58,59]; however, beta-blockers were associated with increased 30-day mortality and the need for mechanical ventilation in patients with CAP.[59] Calcium channel blockers, beta-blockers, and thiazide were associated with a greater risk of 90-day hospitalization with pneumonia.[60] No studies have demonstrated the effect of statins, beta-blockers, calcium channel blockers, and diuretics on decreasing cardiac complications in patients with pneumonia.

Furthermore, specific attention should be paid to medications with cardiovascular side effects for COVID-19, especially in patients with underlying cardiovascular disease. Common antibiotics, which are used for secondary bacterial infections, exert effects on the cardiovascular system. Macrolides (eg, azithromycin)[61] and fluoroquinolone[61] have proarrhythmic effects, which include QT- interval prolongation and polymorphic ventricular tachyarrhythmia. Vancomycin can induce the release of histamine, leading to peripheral vasodilation and severe hypotension.[61] Some formulations of intravenous antibiotics contain a substantial amount of sodium, and attention should be paid to the daily sodium loads, especially in patients with heart failure.[48]

Chloroquine/hydroxychloroquine, which is an old drug for malaria, has been confirmed to be effective in patients with COVID-19.[62,63] However, their cardiotoxicity, which includes arrhythmia, heart failure, and myocardial disorder, may be severe and irreversible.[64]

Anti-inflammatory therapies also have been used in patients with COVID-19. Clinical trials about the effects of tocilizumab, a recombinant IL-6 monoclonal antibody, and baricitinib, an orally administrated selective inhibitor of JAK1 and JAK2, on COVID-19, are recruiting patients. However, both drugs have been proven to be associated with elevated cholesterol levels.[65,66] Although the association between altered lipid levels and cardiovascular risks is not identified, this side effect cannot be dismissed. Anti-PD-1 antibody, as a checkpoint inhibitor, also has been applied in the treatment of COVID-19 (NCT04268537 and NCT04333914). However, its pulmonary, cardiac, and neurologic toxicity, which is usually fatal, should not be underestimated. Glucocorticoids, which can suppress inflammation, have been used as empirical treatment in severely ill COVID-19 patients,[19] and several clinical trials are recruiting patients to evaluate their effectiveness and safety. However, corticosteroid use in patients with SARS,[67] MERS,[68] and influenza[69] did not improve patient outcome. In addition, their use was not recommended as treatment for COVID-19 outside of clinical trials.[70]

Conclusion

COVID-19 is rapidly spreading globally. At present, very little is known about this virus. Before vaccination is available, there is no effective therapy at present. As new clinical evidence emerges, the diagnosis and treatment may change. Clinical trials are necessary to determine the risk factors of cardiac complications, the mechanisms of cardiac injury, and possible treatments to improve the outcome of patients with COVID-19.

Conflict of Interest

None.

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