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Coronavirus disease 2019 and cardiovascular system: A narrative review

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ABSTRACT

At the end of 2019, a viral pneumonia disease called coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), emerged in Wuhan, China. This novel disease rapidly spread at an alarming rate that as a result, it has now been declared pandemic by the World Health Organization. Although this infective disease is mostly characterized by respiratory tract symptoms, increasing numbers of evidence had shown considerable amounts of patients with cardiovascular involvements and these were associated with higher mortality among COVID-19 patients. Cardiac involvement as a possible late phenomenon of the viral respiratory infection is an issue that should be anticipated in patients with COVID-19. Cardiovascular manifestation in COVID-19 patients include myocardial injury (MI), arrhythmias, cardiac arrests, heart failure and coagulation abnormality, ranging from 7.2% up to 33%. The mechanism of cardiac involvement in COVID-19 patients involves direct injury to myocardial cells mediated by angiotensin-converting enzyme 2 (ACE2) receptors as suggested by some studies, while the other studies suggest that systemic inflammation causing indirect myocyte injury may also play a role. Combination of proper triage, close monitoring, and avoidance of some drugs that have cardiovascular toxicity are important in the management of cardiovascular system involvement in COVID-19 patients. The involvement of the cardiovascular system in COVID-19 patients is prevalent, variable, and debilitating. Therefore, it requires our attention and comprehensive management.

Contents

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ACE2, Angiotensin Converting Enzyme-2; MI, Myocardial Infarction; COVID-19, Coronavirus Disease 2019; TnT, Troponin T; LV, Left Ventricle; Hs-cTnI, High-sensitive cardiac troponin I; ARDS, Acute respiratory distress syndrome; CK-MB, Creatine Kinase Myocardial Band; FDP, Fibrin degradation products; DIC, Disseminated intravascular coagulation; VTE, Venous thromboembolism; CVD, Cardiovascular disease; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CPVT, Catecholaminergic polymorphic ventricular tachycardia; PCI, Percutaneous coronary intervention; CFR, Case-fatality rate.

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1. Introduction

The first cases of COVID-19 were reported in December 2019, originating in Wuhan, China [1], and with its rapid spread, COVID-19 has now become a pandemic affecting 972,303 people across more than 170 countries around the world [2].

With the increasing number of confirmed cases and the accumulating clinical data, in addition to the common clinical presentation of respiratory failure caused by COVID-19, the cardiovascular manifestations induced by this viral infection has generated considerable concern. Huang et al. reported that 12% of patients with COVID-19 were diagnosed as having acute myocardial injury, showed by elevated levels of high-sensitive troponin I [3]. From other recent data, among 138 hospitalized patients with COVID-19, 16.7% had arrhythmias and 7.2% had acute myocardial injury [4]. These reports provides evidences of cardiac involvement as a possible late phenomenon of the viral respiratory infection. This process can be subclinical with few interstitial inflammatory cells, as reported by an autopsy study [5], or can present with overt manifestations even without respiratory symptoms [6].

Not only has its number increased, cardiovascular manifestations were also associated with increased mortality among COVID-19 patients. Tao Guo et al. conducted a study on 187 patients with COVID-19, a total of 52 (27.8%) exhibited myocardial injury as demonstrated by elevation of TnT levels, and mortality was markedly higher in patients with elevated Troponin T (TnT) levels than in patients with normal TnT levels (59.6% vs 8.9%). Patients with underlying cardiovascular disease (CVD) and escalation of TnT levels had the highest mortality (69.44%) and the shortest survival term [7]. All of these data suggest that we must also put concern on cardiovascular manifestations in patients with COVID-19 infections. Therefore, here we review the cardiovascular system involvement in the course of COVID-19 infection.

Table 1
Risk Factor of Cardiac Involvement in COVID-19 Patients [8,9,10,11,12,13].

Risk Factors	Author	Results
Older age Hypertension Diabetes Chronic Heart Failure Cancer	Shaw et al. [8] Kwong et al. [9] Shi et al. [12] Oudit et al. [13]	These are the most common risk factors for developing cardiovascular involvement in COVID-19 infection than those with normal levels of Troponin I or Troponin T. These risk factors increase risk of hemodynamic decompensation during severe infectious illness. Diabetic patients are prone to develop more severe illness after contracting SARS-CoV2.
Previous coronary artery disease Atherosclerotic heart disease	Smith et al. [10] Bonow et al. [11]	These factors increase risk of developing acute coronary syndrome during acute infections as seen on previous studies of influenza and other acute inflammatory conditions.

2. Risk factors of developing cardiovascular involvement in COVID-19 infection

Current data from China and Italy as well in the US show that COVID-19 can present in relatively mild symptoms in affected individuals. However, some patients can suffer from very severe or even deadly conditions which require intensive care. Patients with more severe illness also at greater risk of mortality, particularly older individuals with underlying comorbidities including cardiovascular disease [8,9]. Table 1 shows various risk factors from several studies that increases the likelihood of patients developing cardiovascular involvement of COVID-19, both with or without prior cardiovascular disease history.

3. Pathophysiology

Although the exact pathophysiological mechanism underlying myocardial injury caused by COVID-19 is not fully understood, a previous report showed that in 35% of the patients infected, the SARS-CoV genome was positively detected in the heart [13]. As shown in Fig. 1, SARS-CoV binds to cells expressing appropriate viral receptors, particularly ACE2, which is abundant in the heart [14]. Murine models and human autopsy samples demonstrate that SARS-CoV can down-regulate myocardial and pulmonary ACE2 pathways, thereby mediating myocardial inflammation, lung edema, and acute respiratory failure [8]. This raises the possibility of direct damage of cardiomyocytes by the virus. SARS-CoV-2 may share the same mechanism with SARS-CoV because the 2 viruses are highly homologous in genome [1,15]. Some recent studies from China address the unique marked affinity of SARS-CoV-2 for the host angiotensin-converting enzyme 2 (ACE2) receptor, raising the possibility of direct viral infection of vascular endothelium and myocardium [12,16]. Furthermore, two experimental studies proved that SARS-CoV-2 uses ACE2, which is also expressed in the heart, as their receptor for entry into the cell [17,18]. All of this data further suggested that SARS-CoV-2 can have a direct invasion mechanism to the heart.

Another possible mechanism by which SARS-CoV-2 can cause injury to myocardial cells is by inflammation. In the study done by Tao Guo et al. plasma TnT levels were significantly positively linear correlated with plasma high-sensitivity C-reactive protein levels, indicating that myocardial injury may be closely associated with inflammatory pathogenesis [7]. Huang et al. also highlighted that in patients with COVID-19, the imbalance of T helper 1 and T helper 2 responses resulted in a cytokine storm, which leads to myocardial injury. The release of inflammatory cytokines after infection may cause reduction in coronary blood flow, decreases in oxygen supply, destabilization of coronary plaque, and micro thrombogenesis [3]. Chronic cardiovascular disease also may become unstable as a consequence of imbalance between infection-induce increased metabolic demand and reduced cardiac reserve. Acute coronary events in patients with COVID-19 may

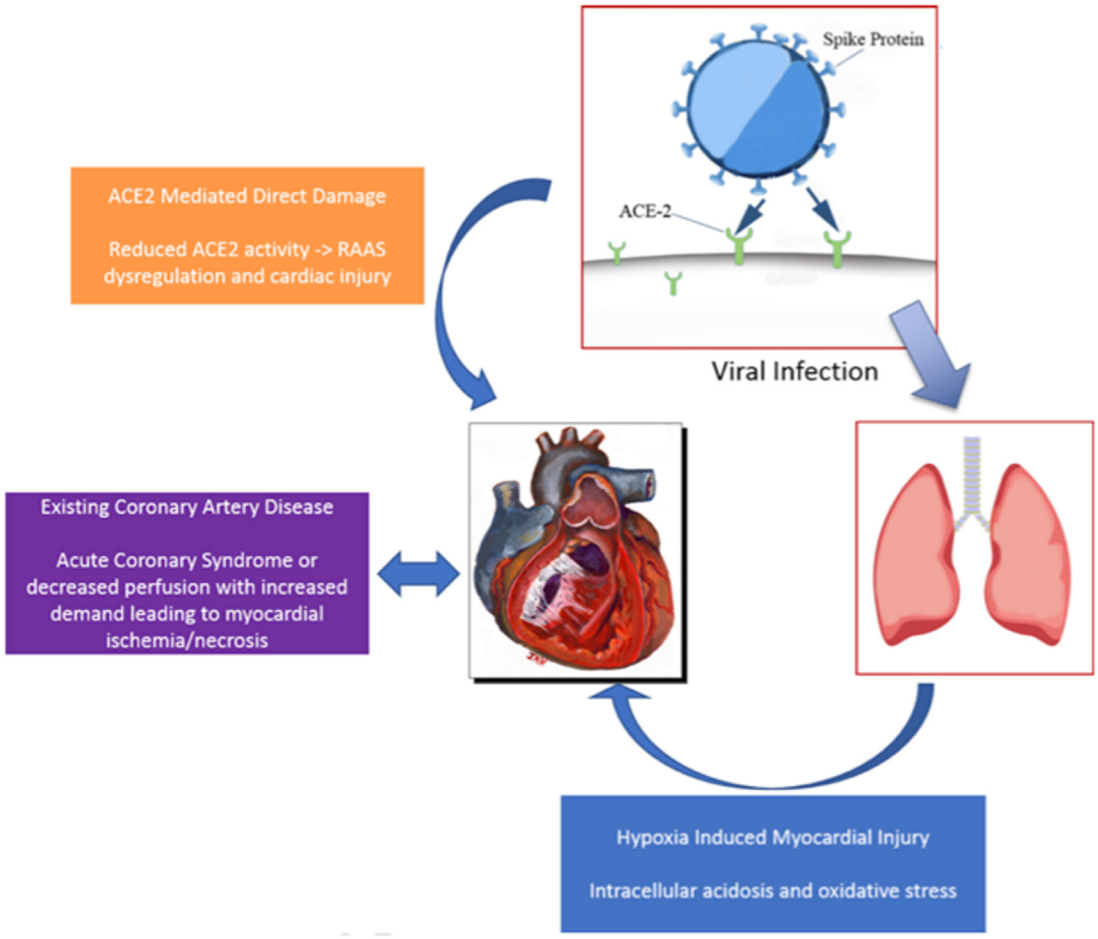

Fig. 1. Possible mechanisms of COVID-19 causing direct myocardial injury via ACE2 [19].

Table 2
Cardiovascular Manifestations and Potential Mechanism [4,20,21].

Manifestations	Potential Mechanism
Acute cardiac injury [21]	Direct myocardial injury, systemic inflammation leads to myocardial oxygen demand supply mismatch, and iatrogenic
Acute coronary event	Inflammation or increased shear stress leads to plaque rupture
Left ventricular (LV) systolic dysfunction	Inflammation or increased shear stress leading to acute LV systolic dysfunction, and can cause acute
Heart failure[20]	decompensation of pre-existing stable heart failure
Arrhythmia	Exact nature not described
Coagulation Abnormalities	Exact nature not described

result from the significant increase in myocardial demand triggered by infections that precipitate myocardial injury or infarct, similar to type 2 myocardial infarction [11].

Patients with coronary artery disease and heart failure may be at particular risk as a result of coronary plaque rupture secondary to virally induced systemic inflammation, therefore, rigorous use of plaque stabilizing agents (aspirin and statins) has been suggested as a possible therapeutic strategy [20]. Coagulation abnormalities and arrhythmias are also seen in patients but the mechanism has yet to be known. Table 2 shows the potential mechanism of each cardiovascular manifestation in COVID-19 patients.

4. Cardiovascular manifestation in COVID-19

4.1. Acute cardiac injury

With severe respiratory infection and hypoxia in the setting of severe respiratory infection and Acute Respiratory Distress Syndrome (ARDS) caused by COVID-19, it is very likely that patients will develop myocardial injury [22]. Myocardial injury associated with the SARS-CoV-2 occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, which mainly manifested as an increase in high-sensitivity cardiac troponin I (Hs- cTnI) levels (>28 pg/ml) [3]. Such finding is associated with more severe disease and worse prognosis [24]. In another report of 138 patients with COVID-19 in Wuhan, 36 patients require intensive care. The levels of biomarkers of myocardial injury were significantly higher in patients treated in the ICU than in those not treated in the ICU (median creatine kinase (CK)-MB level 18 U/l versus 14 U/l, $P < 0.001$; Hs- cTnI level 11.0 pg/ml versus 5.1 pg/ml, $P = 0.004$), suggesting that patients with severe symptoms often have complications involving acute myocardial injury [4]. Another study of critically-ill COVID-19 patients demonstrated that 33% (n = 7) of patients developed cardiomyopathy [23].

4.2. Cardiac arrhythmias

Another common cardiovascular manifestation found in COVID-19 patients are cardiac arrhythmias and cardiac arrest. One of the presenting symptoms in 7.3% of patients admitted for COVID-19 is

Table 3
Outcomes of acute cardiovascular manifestations of COVID-19 infection [3,5,21,23,24].

Author	Cardiovascular manifestations	Outcomes
Huang et al. [3]	Myocardial injury in 5 patients (increase in high-sensitivity cardiac troponin I (Hs- cTnI) levels (>28 pg/ml))	Four patients required intensive care
Wang et al. [5]	Acute myocardial injury (7,2%) and arrhythmia (16,7%)	Most patients requires Intensive care
Arentz et al. [23]	Cardiomyopathy (33%) (Defined as evidence of a globally decreased LV systolic function on transthoracic echocardiogram and clinical signs of cardiogenic shock, an elevation in level of creatinine kinase or troponin I, or a decrease in central venous oxygen saturation (<70%) without a past history of systolic dysfunction.)	High rate of ARDS and a high risk of death
Liu K et al. [24]	Cardiovascular disease (7,3%) (manifested by non-specific heart palpitations)	Respiratory support was required for most of the patients upon admission
Zhou et al. [21]	Coronary heart disease (8%), Heart failure (23%), coagulopathy (19%)	Significantly higher mortality rate

a non-specific heart palpitations, according to a cohort of 137 patients [24]. These symptoms are more common in ICU patients compared to the non ICU patients (44.4% vs 6.9%) although specific types of arrhythmia are not described [4]. Prevalence of arrhythmia might be attributable to metabolic abnormalities, hypoxia, neurohormonal or inflammatory stress in the settings of viral infection whether the patient has preexisting cardiovascular disease or not. Underlying myocarditis should highly be suspected in patients with new onset malignant tachyarrhythmia in the setting of elevated troponin levels [25].

4.3. Heart failure

A report by Zhou and colleagues shows that 23% of COVID-19 patients have heart failures which are notably more common in patients who did not survive hospitalization compared to those who did survive (51.9% vs 11.7%) [21]. When a patient contracts an ARDS, right heart failure often coexists [26]. ARDS usually manifests as ground-glass opacities on chest imaging [27]. Such feature is similar to the case of *de novo* or coexisting pulmonary edema. It is therefore very important to watch out for cardiogenic or mixed cardiac and primary pulmonary causes of respiratory manifestations in COVID-19 (see Table 3).

4.4. Coagulation abnormality

Although there are no published case series so far, there are reports of abnormal coagulation studies in patients with COVID-19 which likely increased risk of venous thromboembolism (VTE) [28]. A multicenter retrospective cohort in China shows that elevated D-dimer levels (>1g/L) in COVID-19 patients were strongly associated with in-hospital death (OR 18.4 95% CI 2.6–128.6, p = 0.003) [21]. Other study comparing survivors to non-survivors' D-dimer and fibrin degradation products (FDP) levels also shows that 71.4% non-survivors met clinical criteria of disseminated intravascular coagulation (DIC) [27]. Risk of VTE and DIC also increases with prolonged immobilization in critically ill patients. Thromboembolic disease should be considered in critically ill COVID-19 patients with clinical deterioration as evidence of hypoxia or hemodynamic instability [6].

5. Consideration of prevention and treatment for cardiovascular complications of COVID-19

The mainstay treatment of COVID-19 is generally symptomatic supportive treatment and intervention. Although currently no specific guidelines regarding the prevention and treatment of cardiovascular complications of COVID-19 have yet to be established, some things have to be taken into consideration when treating these patients.

5.1. Proper triage and close monitoring

It is reasonable to triage patients with COVID-19 according to the presence of underlying CVD and evidence of myocardial injury. This measure is to provide prioritized treatment and more aggressive treatment strategies compared to those without such conditions. Other cardiac biomarkers such as NT-proBNP and electrocardiograms should be closely monitored for early warning and intervention.

5.2. Monitor drug side effects

Many drugs used to treat COVID-19 patients may cause and exacerbate cardiac insufficiency, arrhythmia or other cardiovascular disorders [29]. Hydroxychloroquine sulfate, a less toxic derivative of chloroquine[30] is currently one of the recommended drugs to treat COVID-19 patients. COVID-19 regimens with (hydroxy) chloroquine are usually combined with additional antiviral drugs such as ritonavir and lopinavir. These drugs are potent CYP3A4 inhibiting drugs and their combination is associated with QT-prolongation thus resulting in disturbance of cardiac rhythm. Epinephrine and other similar drugs have been proved in unmasking ventricular arrhythmias [31]. Patients with familial arrhythmias such as catecholaminergic polymorphic ventricular tachycardia (CPVT), when given such drugs may result exacerbation of symptoms. Given that in most cases COVID-19 (around 89.9% in a study by Wang et al.) patients receive antivirals, this the possibility of these side effect must be taken into consideration. Close monitoring using ECG is to be done in patients treated with these drugs.

5.3. Thrombo phylactic

With the likelihood of critically ill COVID-19 patients to develop thromboembolic disease, thrombo phylactic utilization is recommended. It is still unknown which drug is optimal for this purpose. While there is drug-drug interaction between some antiviral therapy and direct oral anticoagulant, low molecular heparins or unfractionated heparin with or without mechanical prophylaxis are suggested and preferred in acutely ill patients [32].

5.4. Reperfusion therapy

In this pandemic settings, the trend of reperfusion therapy intended for STEMI patients has shifted. Fibrinolytic therapy is more preferred than percutaneous coronary intervention (PCI) whenever the facilities and the infrastructure are compatible to deliver the procedure. Each institution should also develop protocols for appropriate triage, isolation, and treatment of COVID-19 patients who may need such interventions [33]. Harm associated

with pursuing reperfusion therapy may exceed the anticipated gain in some COVID-19 patients, particularly if the primary competing illness portends a poor outcome.

6. Prognosis

Underlying medical comorbidities appear to significantly impact COVID-19 severity and mortality. Summary of a report of 72 314 Cases from the Chinese Center for Disease Control and Prevention found that overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44 672 confirmed cases). Patients with underlying cardiovascular disease and hypertension have been reported to have significantly high-case fatality rates (CFR) compared with patients without these underlying comorbidities (10.5 and 6 percent mortality, respectively, compared with 0.9 percent mortality without underlying comorbidities) [34,35].

7. Further research

Significant adverse impact towards cardiac involvement has been posed by this illness but, data available currently regarding the interplay between CVD and COVID-19 are grossly inadequate.

So far, literatures studying the pathophysiological mechanisms of how SARS-CoV2 can affect the cardiac are still very limited. Researchers mostly used SARS as a comparison model for it is very similar to SARS-CoV-2. It is essential to understand this topic for such knowledge will give us better insight of the virus. Another interesting field for further research is the treatment of this disease. Up until now, most regiments currently used to combat COVID-19 and other similar diseases such as SARS mainly aim to provide supportive care. However, a new drug which may specifically inhibit viral growth is being developed. The drug is recombinant angiotensin converting enzymes (ACE2) which works mostly as a decoy towards the virus' S receptors. While the research has so far been limited to cell cultures and organoids, this new drug seems to be promising. A drug as such, if successfully developed, will hypothetically decrease the mortality, morbidity, and even prevent the cardiovascular manifestations of COVID-19.

Acknowledging the lack of data we have, it is therefore highly desirable that the mechanisms, the clinical presentation, the outcomes of various CV manifestations and the proper treatment in these patients be studied further.

8. Conclusion

Finally, it is concluded that SARS-CoV-2 has a devastating impact on the cardiovascular system. Thus, these patients require clinician's meticulous attention towards the cardiovascular system and comprehensive treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Consent

No consent from patients was needed regarding this type of study because this study did not involve the process of collecting data from patients.

Ethical Approval

No ethical approval was needed regarding this type of study because this study did not involve animal projects.

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