Coronavirus Disease 2019 and Cardiovascular Disease: Does This Novel Disease Directly Affect the Cardiovascular System?

Shoji Haruta*
Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center, Chiba, Japan

Abstract
The coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused a global pandemic. The worsening of COVID-19 is caused by viral pneumonia, but the disease also remarkably affects the cardiovascular system. This paper discusses the relationship between COVID-19 and cardiovascular diseases reported in the literature. Reports have indicated that patients with cardiovascular risk factors are more likely to contract COVID-19, and that contracting COVID-19 is more likely to induce cardiovascular diseases and worsen the disease. Further elucidation of the pathology of cardiovascular diseases caused by COVID-19 is expected to result in the development of treatment in the future.

Keywords: Cardiovascular diseases; COVID-19; SARS-CoV-2

Introduction
The novel coronavirus disease (COVID-19), which emerged in Wuhan, China at the end of 2019, caused a global pandemic, and as of July 30, 2020, the number of infected individuals worldwide was 17.04 million, number of deaths was 667,218 and mortality rate was 3.9%. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The main pathology of COVID-19 is viral pneumonia, but the disease remarkably affects the cardiovascular system. Patients with arteriosclerotic and Cardiovascular Diseases (CVDs) are characterized by tendencies to have exacerbated conditions when contracting COVID-19. Furthermore, CVD onset in patients with COVID-19 can render them in critical condition and increase the mortality rate. The epicenter of the COVID-19 outbreak was in China, so most COVID-19-related papers and reports have been from this region. However, a systematic comparison between these reports and other subsequent reports from overseas is lacking, and a precise analysis of data is warranted because of the effect of various factors including the prevalence of existing risk factors, selection bias, hospitalization thresholds, and treatment methods on previous findings. This paper discusses the relationship between COVID-19 and CVDs reported in the literature.

Sars-Cov-2 and other Coronaviruses
The novel SARS-CoV-2, which causes COVID-19, is a single-stranded envelope RNA virus and is the seventh human coronavirus that has been discovered. Unlike other coronaviruses that are known to cause colds (229E, OC43, NL63 and HKU1), this virus shares similarities with the zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV), which has caused Severe Acute Respiratory Syndrome (SARS) since 2002, and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which has caused Middle East Respiratory Syndrome (MERS) since 2002 [1]. SARS-CoV and MERS-CoV can cause cardiovascular complications, but there has been virtually no systematic research on the topic (Table 1). Research on 121 patients with cardiovascular complications caused by SARS-CoV showed that hypertension occurred in 61 hospitalized patients (50.4%), and of these patients, 71.9% developed persistent tachycardia, with 40% of these patients experiencing persistent tachycardia even during the outpatient follow-up. SARS-CoV infection is correlated with numerous CVDs, but there have been no clear case reports on myocarditis [2-10].

Meanwhile, a report on an outbreak in Saudi Arabia in 2012 reported the onset of acute myocarditis and heart failure due to MERS-CoV [6]. Measurements of the now frequently used troponin have not been conducted in reports on either SARS-CoV or MERS-CoV with regard to symptoms, electrocardiogram findings, radiographic findings, and echocardiographic findings as indicators of myocardial damage.

SARS-CoV-2 and Angiotensin-Converting Enzyme 2
SARS-CoV-2 infection is caused by the activation of spike proteins due to Transmembrane Protease, Serine 2 (TMPRSS2), followed by the binding of viral surface spike proteins to Angiotensin-Converting Enzyme 2 (ACE2) receptors [11]. ACE2 receptors expressed in the lungs (primarily alveolar type II cells [12]) are the primary source of entry for the virus. ACE2 receptors are also highly expressed in the heart and blood vessels, counteracting the effects of angiotensin II and causing excessive activation of the renin-angiotensin system,
including hypertension, Congestive Heart Failure (CHF) and atherosclerosis.

ACE2 receptors in animal models are upregulated by hypertension and Angiotensin-Converting Enzyme (ACE) inhibition [13], and susceptibility to coronavirus infection theoretically increases. Meanwhile, it has been suggested that ACE2 receptors may have protective properties. Genetic inactivation of ACE2 receptors caused severe lung injuries in mice infected with avian influenza, and the reconstitution of ACE2 receptors reduced the observed injuries [14]. Social media has amplified these considerations, and concerns in the medical community have been raised regarding the use of ACE inhibitors, Angiotensin Receptor Blockers (ARBs), and angiotensin receptor-neprilysin inhibitors in patients at risk of contracting COVID-19 [15]. However, most major international cardiology associations, including the American College of Cardiology, American Heart Association, Heart Failure Society of America, and the European Society of Cardiology have stated that there were insufficient data on the increased risk of SARS-CoV-2 infection from the use of ACE inhibitors, ARBs, and angiotensin receptor-neprilysin inhibitors in patients undergoing treatment with these drugs, and that their administration should be continued in patients independent of COVID-19 risk or infection [16,17]. This issue is currently under investigation, but for the time being, experts advise that the removal of these drugs from patients with heart failure or previous myocardial infarction may lead to adverse results and clinical decline [18].

Covid19 and Comorbid Disorders

CVD was a common comorbid disorder in previous SARS and MERS patients (Table 2). The prevalences of diabetes and CVDs in SARS were 11% and 8%, respectively, and the risk of death in the presence of either comorbid disorder increased by a factor of 12 [6,19]. Diabetes and hypertension were observed in approximately 50% of patients with MERS, and CVDs were observed in 30% [1]. The increased comorbidity of CVD also applies for patients with COVID-19, particularly in patients with more severe conditions. A large study performed by the Chinese Center for Disease Control and Prevention reported that for clinical severity among 72,314 patients suspected of having COVID-19 (44,672 patients tested and confirmed, 16,186 patients suspected, 10,567 patients clinically diagnosed), 81.4% showed mild symptoms, 13.9% showed severe symptoms, and 4.7% were in critical conditions [20]. Of the patients confirmed in this study, 12.8% had hypertension, 5.3% had diabetes, and 4.2% had CVD. These prevalences are lower than that of CVD risk factors in typical Chinese populations, but they were not age-adjusted; thus, care must be taken in interpretation of the data given the fact that 53% of patients lacked data relating to comorbid disorders [21]. A study of 5,700 patients in Westchester County, Long Island, New York (USA) reported comorbid disorders of hypertension (56.6%), obesity (41.7%), diabetes (33.8%), coronary artery disease (11.1%) and CHF (6.9%) [22]. Compared to these data, the prevalences of hypertension, obesity, and diabetes in a general United States population were 45%, 42.4%, and 10.5%, respectively [23-25]. An early-stage retrospective analysis based on data for 138 patients in Wuhan, China indicated that approximately 50% of patients infected with COVID-19 had at least one comorbid disorder [26]. Furthermore, this percentage was high among patients with severe COVID-19 infection, at 72% [26]. The correlations between COVID-19 and diabetes, hypertension, and CVD are currently unclear, but the mechanisms are thought to be due to some kind of risk factor for COVID-19 in patients with CVDs, including senior age in patients with advanced CVD, immune system dysfunction and elevated ACE2 levels.

Covid19 and Acute Myocardial Injury

Myocardial injury is defined as an increase in the cardiac Troponin I (TnI) or Troponin T (TnT) above the 99th percentile of upper reference limits (Table 3). Myocardial injuries occur as ischemic or non-ischemic processes [32,33]. Advances in troponin assays have led to the detection of elevated troponin levels without clear symptoms or signs of myocardial ischemia, and the fourth universal definition of myocardial infarction separates it from non-ischemic myocardial injury [34]. The correlations between viral infection and myocardial injury are well known, and most commonly include adenoviruses and enteroviruses such as coxsackievirus [35]. Previous influenza and coronavirus outbreak data showed that both viruses caused myocarditis and myocardial injury [10,36].

<table>
<thead>
<tr>
<th>Virus</th>
<th>First author</th>
<th>Number of patients</th>
<th>Cardiac manifestations</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV</td>
<td>Yu et al., [2]</td>
<td>121</td>
<td>Tachycardia (72%)</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypotension (50%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bradycardia (15%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cardiomegaly (11%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Li et al., [4]</td>
<td>46</td>
<td>Subclinical diastolic dysfunction without systolic impairment</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>Booth et al., [6]</td>
<td>144</td>
<td>Pulse=100bpm (46%)</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chest pain (10%)</td>
<td></td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>Assiri et al., [7]</td>
<td>47</td>
<td>Chest pain (15%)</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Saad et al., [8]</td>
<td>70</td>
<td>Arrhythmia (16%)</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>Al-Tawfiq et al., [9]</td>
<td>17</td>
<td>Cardiomegaly (53%)</td>
<td>76%</td>
</tr>
<tr>
<td></td>
<td>Alhogbani [10]</td>
<td>1</td>
<td>Chest pain (7%)</td>
<td>Recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute myocarditis and acute heart failure</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Cardiovascular complications associated with SARS-CoV and MERS-CoV.

SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; bpm, beats/min; ND, no documented.
A series of papers investigated the correlations between COVID-19 and myocardial injury, but most of them were from China during the early stages of the pandemic. Differences in the region-dependent existing risk factor, prevalence, age distribution, subject selection bias, hospitalization threshold, treatment standard, and form of novel coronavirus are thought to be important factors for data interpretations, but at the current stage, only existing reports can be analyzed when considering the correlations between COVID-19 and myocardial injury. A review by Bavishi et al., of 26 clinical trials comprising more than 100 patients with COVID-19 (data up until May 20, 2020 were published) reported that in 11,685 patients with COVID-19, the overall prevalence of acute myocardial injury ranged between 5% and 38% depending on the standards used, with an overall prevalence of 21.4% [39]. The magnitude of increases in cardiac troponin may be correlated with the disease severity and prognosis severity [40]. Reports by Shi et al. showed that a creatine kinase-MB level >2.2 ng/mL (hazard ratio, 4.56; p=0.02) were independently correlated with increases in the hospital mortality rate [41]. A prospective cohort study by Du et al., indicated that among 179 patients with COVID-19 pneumonia, a TnI level >0.026 ng/mL (hazard ratio, 4.56; p=0.02) were independently correlated with increases in the hospital mortality rate [42].

Table 2: Relative frequency of CV risk factors or underlying CV conditions in available COVID-19 cohorts and representative parent populations.

<table>
<thead>
<tr>
<th>First author</th>
<th>Location</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>CV risk factors</th>
<th>Findings of myocardial injury</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al., [27]</td>
<td>China</td>
<td>1,099</td>
<td>-</td>
<td>7.3</td>
<td>15.0</td>
<td>14.4</td>
</tr>
<tr>
<td>Zhou et al., [28]</td>
<td>China</td>
<td>191</td>
<td>-</td>
<td>18.8</td>
<td>30.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Wang et al., [26]</td>
<td>China</td>
<td>138</td>
<td>14.5</td>
<td>10.1</td>
<td>31.2</td>
<td>-</td>
</tr>
<tr>
<td>Huang et al., [29]</td>
<td>China</td>
<td>41</td>
<td>14.6</td>
<td>19.5</td>
<td>14.6</td>
<td>-</td>
</tr>
<tr>
<td>Ruan et al., [30]</td>
<td>China</td>
<td>150</td>
<td>8.7</td>
<td>16.7</td>
<td>34.7</td>
<td>-</td>
</tr>
<tr>
<td>Wu et al., [31]</td>
<td>China</td>
<td>201</td>
<td>4.0</td>
<td>10.9</td>
<td>19.4</td>
<td>-</td>
</tr>
<tr>
<td>Wu et al.* [21]</td>
<td>China</td>
<td>44,672</td>
<td>4.2</td>
<td>5.3</td>
<td>12.8</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3: Selected studies reporting cardiac markers and acute myocardial injury in patients with COVID-19.

<table>
<thead>
<tr>
<th>First author</th>
<th>Location</th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>CV risk factors</th>
<th>Findings of myocardial injury</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al., [26]</td>
<td>China</td>
<td>118</td>
<td>56</td>
<td>HTN 31%</td>
<td>DM 10%</td>
<td>Troponin I level &gt;28 pg/ml or new EKG/echo changes, 7.2%</td>
</tr>
<tr>
<td>Zhou et al., [28]</td>
<td>China</td>
<td>191</td>
<td>56</td>
<td>HTN 30%</td>
<td>DM 19%</td>
<td>Troponin I level &gt;28 pg/ml, 17%</td>
</tr>
<tr>
<td>Shi et al., [37]</td>
<td>China</td>
<td>416</td>
<td>64</td>
<td>HTN 31%</td>
<td>DM 14%</td>
<td>Troponin I level (μg/l)&gt;99th percentile, 19.7%</td>
</tr>
<tr>
<td>Guo et al., [38]</td>
<td>China</td>
<td>187</td>
<td>59</td>
<td>HTN 33%</td>
<td>DM 15%</td>
<td>Troponin I level (μg/l)&gt;99th percentile, 27.8%</td>
</tr>
<tr>
<td>Richardson et al., [22]</td>
<td>US</td>
<td>5,700</td>
<td>63</td>
<td>HTN 56.6%</td>
<td>DM 33.8%</td>
<td>Troponin I and T levels (including hs-troponin) &gt;the upper limit of normal, 22.6%</td>
</tr>
</tbody>
</table>

COVID-19, coronavirus disease; HTN, Hypertension; DM, Diabetes Mellitus; CAD, Coronary Artery Disease; US, United States; CV, Cardiovascular; EKG, Electrocardiographic; echo, echocardiographic; hs-troponin, high-sensitivity troponin.
with CVD tended to have higher TnT values than those without CVD (54.5% versus [vs.] 13.2%). The mortality rates during hospitalization were 7.62% in patients without CVD and normal TnT levels, 13.33% in those with CVD and normal TnT levels, 37.50% in those without CVD and elevated TnT levels, and 69.44% in those with CVD and elevated TnT levels. When compared to those with normal TnT levels, patients with elevated TnT levels were older (71.4 vs. 53.5 years, \( p < 0.001 \)) and more commonly male (65.4% vs. 42.2%, \( p = 0.005 \)). Additionally, the percentages of patients with underlying diseases such as hypertension (63.5% vs. 20.7%, \( p < 0.001 \)), coronary artery disease (32.7% vs. 3.0%, \( p = 0.001 \)) and cardiomyopathy (15.4% vs. 0%, \( p < 0.001 \)) were significantly higher in those with elevated TnT levels than in those without. Plasma TnT levels were significantly positively correlated with high-sensitivity C-reactive Protein (CRP) (\( \beta = 0.530 \), \( p < 0.001 \)) and N-terminal pro-B-type natriuretic peptide levels (\( \beta = 0.613 \), \( p < 0.001 \)). CRP (8.55 vs. 3.13mg/dL, \( p < 0.001 \)), procalcitonin (0.21 vs. 0.05ng/mL, \( p < 0.001 \)), and globulin levels (29.7 vs. 27.24g/L, \( p < 0.001 \)) were significantly higher in the cardiomyopathy group than in the non-cardiomyopathy group. Respiratory failure was more advanced in the cardiomyopathy group than in the non-cardiomyopathy group, with both arterial oxygen partial pressure (PaO2) (64.0 vs. 91.0mmHg, \( p < 0.001 \)) and PaO2/fraction of expired oxygen (153.3 vs. 390.5mmHg, \( p < 0.001 \)) being significantly lower and more patients requiring mechanical ventilation (59.6 vs. 10.4%, \( p < 0.001 \)).

No assessment has been conducted for myocardial injury due to troponin measurements in asymptomatic or mild and non-hospitalized patients with COVID-19. Further, it is difficult to grasp the full range of myocardial injuries due to COVID-19.

**Mechanism of myocardial injury in COVID-19**

The mechanisms of myocardial injury in patients with COVID-19 remain uncertain, but possible mechanisms are as follows. (1) Type 2 myocardial infarction, imbalance of the myocardial oxygen supply and demand due to tachycardia, hypotension and pneumonia-induced hypoxemia; (2) acute coronary syndrome due to acute atherothrombosis in a viral thrombotic and inflammatory environment; (3) microvascular dysfunction due to microthrombosis or vascular injury; (4) stress-induced cardiomyopathy (Takotsubo syndrome); (5) non-ischemic myocardial injury due to an inflammatory cytokine storm; (6) direct viral cardiomyocyte toxicity and myocarditis; and (7) cardiovascular disorders caused by antiviral agents. Direct cardiovascular disorders due to SARS-CoV-2 include (2), (3), and (6), but multiple mechanisms may contribute to myocardial injury in a single patient as well. In patients in whom CVD exists as a comorbid disorder, (1) is thought to contribute to myocardial injury. In actuality, it is extremely difficult to distinguish between these mechanisms in critical conditions, but there is a possibility that treatment methods may vary widely depending on whether the etiology is coronary plaque rupture, inconsistent oxygen supply, pathogen/endotoxin relationships, cytokine storm, or a combination of active oxygen radicals induced by the infection process [43].

**Chronic Heart Disease and Covid-19**

It is still unknown whether chronic heart problems remain after recovery from COVID-19. Research results from the chronic outcome of SARS-CoV, which is structurally similar to SARS-CoV-2, serve as a reference here. A longitudinal study of patients who recovered from SARS-CoV reported that among patients who recovered, 68% exhibited hyperlipidemia, 4% exhibited CVDs, and 60% exhibited impaired glucose metabolism [44]. Lipid metabolism and serum concentrations of free fatty acid, lysophosphatidylcholine, lysophosphatidylethanolamine, and phosphatidylglycerol were significantly increased in patients with a medical history of SARS-CoV infection compared to those without such a history. These results suggest that SARS-CoV is correlated with CVDs and changes in serum metabolism. Chronic heart disease as a coronavirus-related pathology needs to be considered based on these findings, and further investigations of heart disease after COVID-19 are necessary.

**Covid-19 And Vascular Disease**

Vascular endothelial cells control blood flow, vasomotor tone, osmotic balance, and vascular barrier function [45,46]. Endothelial cells play an important role in most human viral infections in enhancing immune responses, inducing increased tissue permeability and inflammation. These responses are associated with the severity of viral infections [47]. Endothelial dysfunction is strongly involved in organ dysfunction during viral infections and induces hypercoagulability, microvascular leakage and organ ischemia [48]. Histopathological findings of SARS-CoV-2 infection highlight the key role of endothelial cells in vascular dysfunction, inflammation and (immune) thrombosis [49]. Varga et al., reported the presence of viral inclusion structures in endothelial cells in three patients infected with SARS-CoV-2, as well as inflammation with aggregation of neutrophils and mononuclear cells in endothelial cells of different organs including the kidney, lung, heart and liver. They suggest that COVID-19-induced endothelitis may explain systemic microcirculatory dysfunction in different organs of COVID-19 patients [49].

Ackermann et al., compared lung samples obtained during necropsy of seven patients who died due to COVID-19, and those during necropsy of seven patients who died due to ARDS secondary to influenza A (H1N1) infection. In the lungs of COVID-19 patients, a unique image of severe vascular endothelial damage accompanied by intracellular SARS-CoV-2 and cell membrane destruction was observed. Histological analysis of pulmonary vessels in COVID-19 patients showed extensive thrombosis with microangiopathy, and these patients had a 9-fold higher prevalence of microthrombus in alveolar capillaries than influenza patients (P<0.001) [50].

In pediatric patients with COVID-19, the possibility of developing Kawasaki disease-like vasculitis has been reported. Verdoni et al., investigated the incidence and clinical characteristics of Kawasaki disease-like patients diagnosed during the COVID-19 pandemic [51]. Patients presented with these symptoms at more than 30 times the monthly incidence in the 2 months of the COVID-19 pandemic compared to that in the last 5 years, with more frequent cardiac disorders and Macrophage Activation Syndrome (MAS). Furthermore, the incidence of severe Kawasaki disease was high. It has also been reported that the incidence of cerebral infarction in COVID-19 patients is increasing. Oxley et al., reported a summary of five patients under the age of 50 years, who visited the US Mount Sinai Health System for cerebral infarction due to large vessel occlusion during the two weeks from March 23 to April 7, 2020 [52]. However, all cases were infected with SARS-CoV-2. In the past 12 months, the average number of patients with cerebral infarction due to major vascular occlusion under the age of 50 in the same two weeks was 0.73. The relationship between COVID-19 and cerebral infarction, due to macrovascular occlusion, in younger age groups needs to be further investigated.
Furthermore, many cases of venous thrombosis in severe COVID-19 patients have been reported. In these cases, an elevated D-dimer level and hypercoagulability were observed, and venous thrombosis frequently occurred in association with these findings [53,54]. As a result of an observational study conducted by Nahum et al., of the Centre Cardiologique du Nord Saint Denis France, the incidence of deep vein thrombosis was high (79%), suggesting that early detection and rapid initiation of anticoagulant therapy may improve the prognosis [55]. Treatment of COVID-19 seems to require integrated therapy of blocking SARS-CoV-2 invasion, immunomodulatory therapy and antithrombotic therapy.

Conclusion

Findings relating to COVID-19 are accumulating on a daily basis, and these require updates with the latest information. However, some papers are rapidly published and revised later. Furthermore, many of these studies are retrospective observational studies, and careful examination of their findings is necessary. With regard to the correlations between COVID-19 and myocardial injury, prospective studies that consider the contributions of old age and comorbid disorders need to be conducted. Clarification of the direct mechanisms of myocardial injury in SARS-CoV-2 would result in the development of therapeutic drugs in the future, determination of the suitability of using existing ACE inhibition and ARBs, and development of new myocardial protective therapies.

Conflicts and Interest

The author declares no conflict of interest.

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