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## CLINICAL REVIEW

# COVID-19 and Interaction with the Cardiovascular System

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### **Introduction**

On December 31st, 2019, public health authorities in China informed the World Health Organization about a cluster of cases of unexplained pneumonia occurring in Wuhan, China.<sup>1</sup> The cases were soon discovered to be caused by a novel coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a distinct virus from that which caused the 2003 SARS outbreak.<sup>2</sup> The disease the virus caused was named COVID-19. The epidemic progressed rapidly from the time it was first described, and on January 19th, 2020 the first case in the United States was reported.<sup>3</sup> Since the initial epidemic in China, COVID-19 has progressed to a pandemic, with both Europe and the United States being heavily affected.<sup>4,5</sup> COVID-19 has a wide spectrum of disease, ranging from asymptomatic cases to severe disease progressing to acute respiratory distress syndrome and shock.<sup>6,7</sup> Heart disease has been described to be both a risk factor for worsened disease, and a sequelae of COVID-19. We therefore reviewed the literature to describe the interaction between the cardiovascular system and COVID-19.

### **Epidemiology of COVID-19 in Patients with Cardiovascular Disease**

The initial experience of COVID-19 in China suggested that patients with comorbidities such as hypertension or heart disease were at greater risk of more severe disease.<sup>7</sup> In patients admitted to intensive care units in Seattle, WA and Lombardy, Italy, 68-86% of patients had at least one comorbidity, of which hypertension was the most common.<sup>5,8</sup> A study of 4,103 patients with COVID-19 in New York City found that heart failure was also a strong predictor of need for hospitalization with an odds ratio of 4.3 95% CI, 1.9-11.2.<sup>9</sup> The only factors with a greater odds ratio for hospitalization were age >65 years or BMI >40. In patients who needed hospitalization, 44.6% had pre-existing cardiovascular disease (which was defined as hyperlipidemia, hypertension, coronary artery disease, or heart failure), compared to 16.3% in those who did not need admission. Interestingly, heart disease did not predict critical illness, which was more highly associated with age >65, and initial labs such as CRP and d-dimer. In contrast, the early experience in Wuhan found hypertension and cardiovascular disease were more common in patients requiring ICU care (58.3% vs 21.6%, and 25.0% vs 10.8%, respectively).<sup>10</sup>

### **Cardiac Manifestations of COVID-19**

In addition to pre-existing cardiovascular disease acting as a risk modifier in patients with COVID-19, infection with SARS-CoV-2 also has been demonstrated to have deleterious effects on the heart and vascular system. This is more prominent in the critically ill. Several small case series reporting early experience of intensive care unit (ICU) patients with COVID-19 found a rate of 0-33% of new-onset cardiomyopathy or 12-22% with cardiac injury (as defined by elevated cardiac enzymes).<sup>8,10-12</sup> While elevation in cardiac enzymes may be demand ischemia due to viral pneumonia and sepsis, cardiac injury has been shown to be associated with subsequent mortality in COVID-19.<sup>13,14</sup>

Stages of COVID-19 that have been proposed include an early flu-like illness, a viral pneumonia stage which can include hypoxia, and a later stage in which systemic hyperinflammation is present.<sup>15</sup> It may be the latter stage in which extrapulmonary organ involvement (including cardiac) first manifests. Multiple cases of severe COVID-19 associated myocarditis or myopericarditis have been described.<sup>16-18</sup> In one of these cases, a 37-year-old patient presented with chest pain, dyspnea, and hypotension.<sup>16</sup> The electrocardiogram revealed ST-elevation in the inferior leads, and CT coronary angiography was negative for coronary stenosis. Troponin T was elevated to more than 10 ng/mL, and echocardiogram revealed a dilated left ventricle (LV) with LV ejection fraction (EF) of 27%. Following treatment with glucocorticoids, intravenous immunoglobulin (IVIG), and supportive care, the cardiac size and function recovered to normal after one week. Another case described the development of shock due to cardiac tamponade in a patient with COVID-19 with immediate improvement following pericardiocentesis.<sup>17</sup> Myocarditis resulting in reverse Takotsubo syndrome was described in another patient.<sup>18</sup> In this case, endomyocardial biopsy (EMB) confirmed myocardial lymphocytic infiltration, although SARS-CoV-2 RNA was not detected. However, another patient with COVID-19 associated myocarditis that underwent EMB was found to have interstitial and endocardial macrophages with direct visualization of viral particles by electron microscopy.<sup>19</sup> Acute cor pulmonale resulting in shock, hemodynamic collapse, and cardiac arrest has also been described in several patients.<sup>20</sup> This was suspected to be due to pulmonary embolism but this was not confirmed in all patients. One echocardiography series found 31% of hospitalized patients with COVID-19 had right ventricular dilation, which was associated with mortality.<sup>21</sup>

There have been two described COVID-19 cases in orthotopic heart transplant recipients (OHT).<sup>22</sup> One patient had mild disease with fever for two days followed by fatigue and poor appetite. The other was hospitalized with severe disease requiring facemask oxygen. After a course of steroids, IVIG, and supportive care, he was eventually weaned off oxygen and was discharged one month after admission. It is not yet clear how OHT modifies the risk of COVID-19. While immunosuppression raises risk of infection, some hypothesize that attenuation of the hyperinflammatory response of COVID-19 with immunosuppression could be protective.<sup>23</sup>

The first known death in the United States due to COVID-19 was a 57-year-old female who was found on autopsy to have died of myocardial rupture.<sup>24</sup> The autopsy revealed myocarditis and “transmural myocardial ischemia” resulting in rupture of the left ventricle. Notably, despite the pathologic finding of transmural ischemia, there was no evidence of coronary atherosclerosis or thrombosis.

### ***Effects of Renin-Angiotensin-Aldosterone System Inhibitors***

The SARS-CoV-2 virus uses the spike protein to bind the ACE2 enzyme which is expressed in cells from multiple organs, most importantly alveolar epithelial cells.<sup>25</sup> The ACE2 enzyme’s primary action is to convert angiotensin II into angiotensin-(1-7). Because the Renin-Angiotensin-Aldosterone System (RAAS) is a target for pharmacologic therapy in heart disease and hypertension, the utilization of ACE2 by SARS-CoV-2 is relevant to patients with cardiovascular disease. Angiotensin II (AT2) is a vasoconstrictor and profibrotic peptide. There is conflicting evidence on the effect of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) on ACE2, however some animal studies show upregulation of ACE2 with both drug classes.<sup>26</sup> This has been hypothesized to have either a protective or deleterious effect on COVID-19 severity. The concern for worsened severity of SARS-CoV-2 infection arises from the fact that upregulation of ACE2 would provide further sites for viral entry into host cells.<sup>25</sup> However, downregulation of ACE2 by SARS-CoV-2 may also result in acute lung injury, possibly due to the deleterious effects of angiotensin II that is no longer being converted to angiotensin-(1-7). Additionally, the cardioprotective effects of ACE2 may be reduced in the setting of downregulation. The direct inhibition of AT2 by ARBs may also prevent the negative effects it has on the lungs.

Early in the epidemic, concerns were raised about continuing patients who were on ACE-inhibitors or ARBs.<sup>27</sup> Although hypertension is associated with the development of severe disease, ACE-I or ARB use is a potential confounder. Major medical societies including the American College of Cardiology, American Heart Association, and the European Society of Cardiology responded by issuing statements supporting continuation of ACE-Is and ARBs in patients who were already taking them.<sup>25,27</sup> Several recent studies have sought to clarify the presence of an association between ACE-I/ARB use and mortality.<sup>28,29</sup> One of these studies found that in-

hospital mortality in 362 patients with hypertension was similar between patients taking and those not taking ACE-Is or ARBs.<sup>27</sup> The other study of 1128 hospitalized COVID-19 patients with hypertension found that mortality was nearly three-fold higher in those not taking ACE-Is or ARBs.<sup>29</sup> These findings, while non-randomized, seem to support society recommendations to continue ACE-Is and ARBs. Randomized controlled trials of losartan in both inpatients and outpatients with COVID-19 are currently recruiting.<sup>30</sup>

### ***COVID-19 and Thrombosis***

As COVID-19 cases have dramatically increased worldwide, thrombosis has emerged as a potential complication of the disease. Autopsy series have found evidence of pulmonary thrombotic microangiopathy, which may be due to an underlying endothelialitis and endothelial injury from SARS-CoV-2 infection.<sup>31,32</sup> In one series of critically ill patients with COVID-19, a 25-31% incidence of thrombotic events was reported.<sup>33,34</sup> This included 27% of patients with venous thromboembolism (VTE) and 4% with arterial thromboembolism. All patients in this series were on standard dose thromboprophylaxis. One autopsy study found that 58% of patients had VTE, with pulmonary embolism as the cause of death in 33%.<sup>35</sup> Furthermore, several patients under 50 years of age with no or minimal pre-existing comorbidities have developed large-vessel stroke during SARS-CoV-2 infection, the youngest reported being a 33-year-old woman without underlying health conditions.<sup>36</sup>

Prophylactic doses of heparin, primarily low-molecular weight heparin, are associated with lower mortality in patients with elevated D-dimer levels compared to those not receiving heparin products.<sup>37</sup> Treatment dose anticoagulation is also associated with lower mortality in ventilated patients with COVID-19.<sup>38</sup> However, the American Society of Hematology and Anticoagulation Forum of North America at this time recommend only using prophylactic doses of anticoagulation until randomized trial evidence supporting escalated doses is available.<sup>39</sup> Randomized trials evaluating therapeutic versus prophylactic doses of enoxaparin are currently recruiting.<sup>40</sup> Another currently recruiting trial seeks to compare aspirin, clopidogrel, low-dose rivaroxaban, and statin therapy to standard care.<sup>41</sup>

### ***Mechanical Circulatory Support and COVID-19***

When hemodynamic collapse occurs with COVID-19, multiple therapeutic options are available. Depending on hospital resource availability, age, and other comorbidities, palliative care should be considered. Goals of care discussions should be conducted with hospitalized patients as soon as possible, given the potential for rapid decompensation. Some patients who are critically ill with COVID-19, have received mechanical circulatory support with extracorporeal membrane oxygenation (ECMO). Patients who should be prioritized for ECMO are younger with minimal comorbidities. Indications for venoarterial (VA) ECMO include shock or hypotension despite the use

of vasopressors, often in the setting of cardiomyopathy.<sup>42</sup> Further, the United States Food & Drug Administration (FDA) granted an emergency use authorization for the RP Impella percutaneous right ventricular (RV) assist device in the setting of COVID-19 related RV failure.<sup>43</sup> To our knowledge, there have been no reported cases of this use. Further, it should be noted that no randomized controlled trial level evidence for RP Impella exists to demonstrate an improvement in outcomes in RV failure, and the FDA has released a warning that post-approval studies have shown an increased rate of mortality with RP Impella use.<sup>44</sup>

### ***Cardiac Imaging Findings in COVID-19***

As many patients with SARS-CoV-2 present with cardiopulmonary complaints, echocardiography is widely available and commonly employed to evaluate these patients. One international survey of COVID-19 patients found that in patients without known prior cardiac disease, 49% had abnormalities on echocardiogram of various severity.<sup>45</sup> These were broad in scope, including left ventricular dysfunction (39%), right ventricular dysfunction (33%), evidence of infarction or myocarditis (8%), and elevated pulmonary pressures. While many these abnormalities were considered mild or moderate, 15% of patients had severe abnormalities. Another repeatedly reported finding was increased left ventricular wall thickness, representative of edema in the setting of myocardial inflammation.<sup>46-49</sup> In one case report, a previously healthy 57-year-old man presented with elevated cardiac enzymes, B-type natriuretic peptide and ECG changes. Subsequent echocardiogram showed a reduced ejection fraction with thickened, echo-bright walls of the left ventricle. Cardiac MRI confirmed the presence of interstitial edema and as well as late gadolinium enhancement indicating scarring and fibrosis.<sup>46</sup>

While less readily available, cardiac MRI is better equipped to detect subtle changes in the heart and provide insights into pathology. In one study, 78% of patients had abnormalities on MRI, including many patients who did not need hospitalization, implying milder symptoms.<sup>50</sup> Of these, 60% had inflammation, 32% had late gadolinium enhancement, and 22% had pericardial enhancement. As the median time from diagnosis to MRI was 71 days, this raises the concern for long lasting effects of even mild COVID-19 infections. Patients with COVID-19 have myocardial edema as demonstrated on T2-weighted and myocardial mapping techniques with cardiac MRI.<sup>46,48</sup> The edema reflects inflammation, although it is not entirely clear whether this is from direct viral infection and injury to myocytes versus the body's immune response to the infection. Patients with cardiac MRI-demonstrated edema and inflammation have undergone endomyocardial biopsy (EMB) demonstrating a lymphocytic infiltration, but without SARS-CoV-2 genetic material being recovered.<sup>49</sup> This may provide important insights into the importance of monitoring and if necessary minimizing the body's immune response as it may be the primary driver of cardiac damage.

Of further concern is that patients infected with COVID-19 may show subtle cardiac abnormalities which have an unclear implication for future problems. A single institution study of 18 patients infected with SARS-CoV-2 reported, all patients with normal left ventricular ejection fraction on standard echocardiography. However, 93% had abnormal myocardial deformation (strain) imaging, which can detect subtle abnormalities in myocardial motion in multiple dimensions.<sup>51</sup> Regional strain patterns were the most often abnormal in basal segments in what could be described as "reverse Takotsubo-like," and such patterns were noted in patients even with mild cases of COVID. The long-term significance of these changes is not yet clear.

### ***Cardiac Abnormalities seen in Children with COVID-19***

Reports in recent months have shown that children are usually less symptomatic than adults from the infection caused by SARS-CoV-2 virus. However, an emergence of a severe post-infectious syndrome (3-6 weeks usually after the initial infection) defined as Multisystem Inflammatory Syndrome in Children (MIS-C) with clinical features resembling both Kawasaki disease (KD) and toxic shock syndrome has been reported.<sup>52</sup>

As New York became the epicenter of outbreaks in the United States, hospitals in NY started reporting concerning symptoms in children exposed to SARS-Cov-2 with high degree of cardiovascular compromise, often with circulatory shock, myocardial depression, and coronary involvement. Dufort et al. studied children from New York hospital during the early pandemic with 95 confirmed and 4 suspected MIS-C cases. All presented with subjective fever or chills; 97% had tachycardia, 80% had gastrointestinal symptoms, 60% had a rash, 56% had conjunctival injection, and 27% had mucosal changes. Vasopressor support was needed in 62% of children, 53% had evidence of myocarditis, 80% were admitted to intensive care unit and 2 died.<sup>53</sup>

Cardiac dysfunction is commonly noted in MIS-C and findings include left ventricular (LV) dysfunction, coronary artery aneurysms, arrhythmias, valvular dysfunction, pericardial effusion and elevated cardiac biomarkers.<sup>53</sup> Feldstein et al. studied 183 children with MIS-C from 53 centers in the US. More than half required vasopressor or vasoactive support, 1 in 12 had coronary artery aneurysms and 38% of patients had LVEF (left ventricular ejection fraction) <55%.<sup>54</sup> The incidence of coronary artery changes has varied among different studies ranging from ~9% to 25% and a small number of large coronary artery aneurysms have been reported. It is unclear at this time if the coronary artery aneurysms enlarge after illness onset like seen in KD.<sup>52</sup>

Several echocardiographic changes have been noted in children with MIS-C. A single-center, retrospective study done by Matsubara et al. assessed 28 patients with MIS-C, 20 normal control subjects and 17 patients with classic KD and found that the MIS-C group had lower LVEF, lower right ventricular

systolic function and reduced measure of LV systolic strain and strain rate. There were abnormalities in systolic and diastolic function even in patients with MIS-C with preserved EF which usually improved over medial follow-up of 5 days.<sup>55</sup>

A combination of cytokine storm, systemic inflammation and acute stress are thought to lead to LV dysfunction. The LV systolic function in most cases seemed to recover within 1 to 2 weeks of diagnosis.<sup>56</sup> Due to short-term follow up so far, the long-term implications on myocardial health are unknown. Future larger multicenter MIS-C studies over longer periods of time are needed to assess evolution of cardiac abnormalities over time.

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