

# A Review of the Cardiac and Cardiovascular Effects of COVID-19 in Adults and Children

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*Symptomatic coronavirus disease 2019 (COVID-19) typically affects the respiratory system but can involve the cardiovascular system. Cardiac complications of COVID-19 can result directly from myocarditis or indirectly from numerous other mechanisms. Differentiating between primary and secondary cardiovascular involvement—our focus in this review—may help to identify the long-term effects of COVID-19 on the heart in adults and children. (Tex Heart Inst J 2021;48(3):e207395)*

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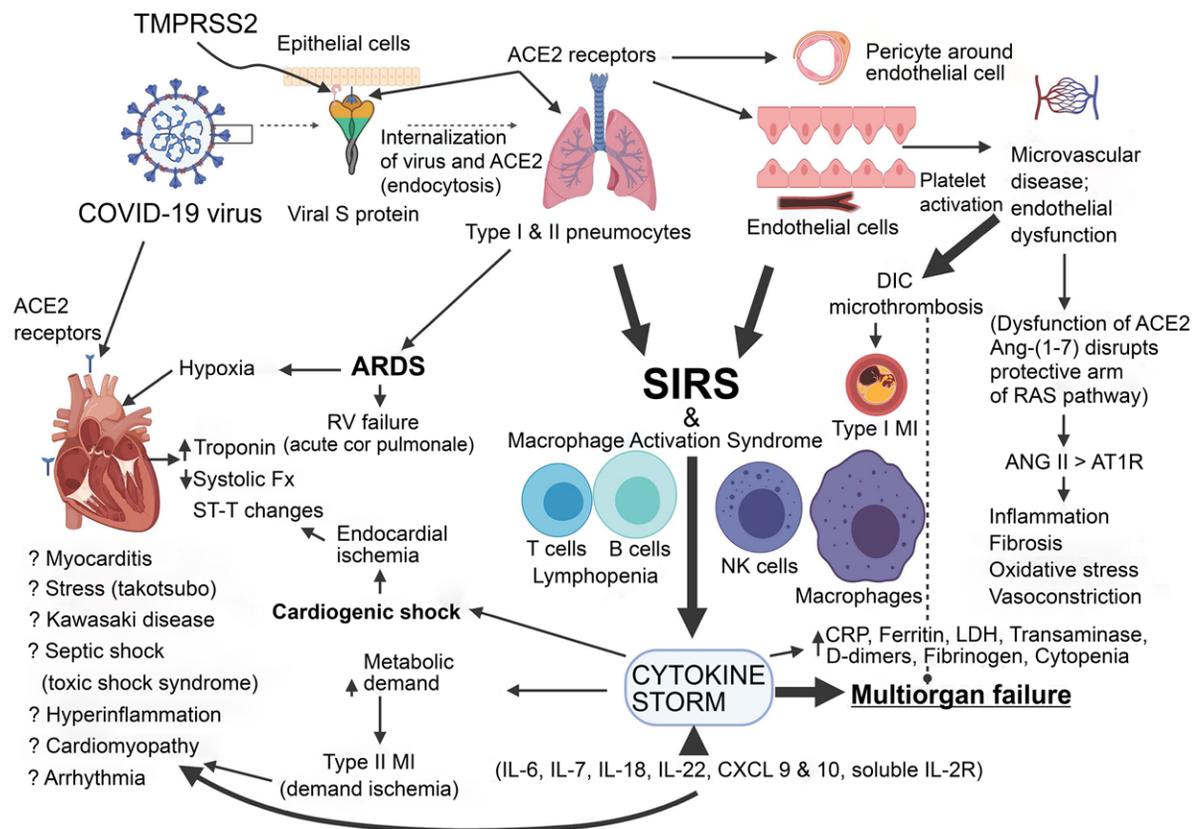
As of late April 2021, more than 148 million cases of coronavirus disease 2019 (COVID-19) had been reported worldwide, and it had caused more than 3.1 million deaths; in the United States, there were 42 million cases and 572,000 deaths.<sup>1</sup> Different countries have reported widely varying case fatality ratios (number of deaths divided by number of confirmed cases) because of differences in the numbers of people tested, demographic characteristics, healthcare delivery systems, and other factors.

The age-dependent susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection leading to symptomatic COVID-19 infection ranges from approximately 20% in children to 70% in older adults.<sup>2</sup> The groups at highest risk of dying of COVID-19 are adults aged 70 years and older (mortality rate, 8%), and people at any age who have substantial comorbidities such as cardiovascular (CV) disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6%), and cancer (5.6%).<sup>3</sup> In the New York City area, the most prevalent comorbidities associated with severe disease and death were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%).<sup>4</sup> Moreover, hospitalized COVID-19 patients with cardiac involvement, defined as elevated troponin (Tn) and other cardiac biomarker levels, seem to have a higher risk of death. However, absent prospective studies, the exact mechanism of inflammation and cardiac involvement is unclear. After our search of the medical literature for cardiac findings in adults and children infected with COVID-19, we present our findings and emphasize the importance of differentiating between primary cardiac and secondary CV involvement.

## The Pathophysiology of COVID-19

A multisystem disease, COVID-19 typically affects the respiratory system and has acute, potentially life-threatening effects on the CV system. Myocarditis, a direct cardiac effect of SARS-CoV-2, occurs through angiotensin-converting enzyme 2 (ACE2) receptors<sup>5</sup>; indirect effects, including acute myocardial ischemia and coronary syndromes, can develop after a cytokine storm induced by the virus (Fig. 1).

The SARS-CoV-2 pathogen is a single-stranded RNA coronavirus that produces its effects through its spike protein and the ACE2 receptors in the alveolar lung cells, vascular endothelium, and cardiac cardiomyocytes.<sup>5</sup> High expression of ACE2 in



**Fig. 1** Diagram shows several potential mechanisms of cardiovascular involvement in coronavirus disease 2019 (COVID-19). (Created with BioRender.com)

ACE2 = angiotensin-converting enzyme 2; ANG = angiotensin; ARDS = acute respiratory disease syndrome; AT1R = angiotensin II type-1 receptor; CRP = C-reactive protein; CXCL = chemokine (CXC motif) ligand; DIC = disseminated intravascular coagulation; Fx = function; IL = interleukin; LDH = lactate dehydrogenase; MI = myocardial infarction; NK = natural killer; RAS = renin-angiotensin system; RV = right ventricular; SIRS = systemic inflammatory response syndrome; TMPRSS2 = transmembrane serine protease 2

pericytes of adult human hearts indicates an intrinsic susceptibility of the heart to SARS-CoV-2 infection.<sup>6</sup> Viral cell entry necessitates that the transmembrane serine protease 2 (expressed on the host cell) perform crucial protein priming that leads to conformational changes, viral cell entry, and cell infection.<sup>7</sup> The virus-receptor interaction results in ACE2 deficiency at the cell membrane from endocytosis that internalizes the virus and the receptor.<sup>8</sup> The absence or the deficiency and downregulation of ACE2, an enzyme that physiologically counters renin-angiotensin-aldosterone system activation, leads to increased angiotensin II activity, which then causes acute heart and lung injury and endothelial cell dysfunction, endogenous catecholamine surge, and cytokine storm.<sup>9</sup> The ACE2 degrades angiotensin II to angiotensin-(1-7) and angiotensin I to angiotensin-(1-9), thereby attenuating its effects on vasoconstriction, sodium retention, and fibrosis.

Existing CV disease predisposes patients to SARS-CoV-2-induced myocardial injury and COVID-19-associated death. In many cases, patients have died from myocardial infarction (MI), heart failure, and ven-

tricular arrhythmias. The specific mechanisms are not known but potentially include cytokine-mediated injury (a systemic cardiotoxic cytokine storm), microvascular injury, and stress-related cardiomyopathy or MI.<sup>10</sup> Occasionally, cytokine storm in adults leads to an acute coronary syndrome caused by plaque rupture (MI type 1) or to cardiogenic shock with decreased myocardial oxygen delivery (MI type 2). Inflammation caused by the influenza virus has been shown to rupture coronary plaque and cause MI.<sup>11</sup>

### Direct Effects of COVID-19 on the Heart

Myocarditis is usually diagnosed by means of established histologic criteria, but this has not been the case in patients with COVID-19. Therefore, myocarditis should be considered in patients with COVID-19 who have acute heart failure, cardiogenic shock, myocardial dysfunction, or elevated Tn levels without coronary ischemia. We found 11 reports of presumptive COVID-19 myocarditis (Table I).<sup>12-22</sup>

In 10 cases,<sup>12-21</sup> diagnoses were made from cardiac magnetic resonance (CMR) findings; in one,<sup>22</sup> endomyocardial biopsy (EMB) samples showed mild inflammation and myofibrillar lysis. Four of the patients (36%) had existing cardiac conditions, and 8 (73%) had abnormal electrocardiographic findings and decreased function on echocardiograms. Cardiac Tn or brain natriuretic peptide (BNP) levels were elevated in all patients tested for these. In the 6 patients who underwent CMR, 3 had myocardial edema on T2 mapping and all had late gadolinium enhancement, suggesting scarring or fibrosis. For the patient who was dead on arrival,<sup>18</sup> autopsy findings included eosinophilic myocarditis, which is atypical in viral myocarditis. Overall, 8 patients recovered, 2 died, and one had an unknown outcome.

The only convincing published evidence of histologically confirmed COVID-19 myocarditis that we found is Tavazzi and colleagues' case report of low-grade myocardial inflammation in the absence of myocardial necrosis, detected in EMB samples.<sup>22</sup> (In differentiating between primary viral myocarditis and secondary myocardial dysfunction, EMB may be considered when the cause of acute coronary syndrome is unclear after

coronary angiography; it is more strongly indicated in patients receiving mechanical circulatory support for cardiogenic shock.) Tavazzi and colleagues<sup>22</sup> observed no viral genome in cardiac myocytes, but did observe viral particles consistent with the coronavirus in macrophages in adjacent interstitial tissue; accordingly, one cannot conclude that SARS-CoV-2 is cardiotropic.

Lindner and colleagues<sup>23</sup> performed autopsies in 39 elderly patients (age range, 78–89 yr) who had COVID-19; virus was found in myocardial tissue samples from 16 of the patients. None had evidence of inflammation or myocarditis. It was unclear whether the patients' age influenced the results.

Puntmann and colleagues<sup>24</sup> identified 100 patients (mean age, 49 ± 14 yr) with COVID-19, 67 of whom recovered at home; the severity of their illness had ranged from asymptomatic to moderate. At a mean time of 71 days after COVID-19 was confirmed, 78 patients had cardiac involvement on CMR, 76 had detectable high-sensitivity TnT, and 60 had evidence of active myocardial inflammation on CMR. All 100 patients had some myocardial involvement regardless of preexisting conditions, the severity or course of infection, the time

**TABLE I. Reports of Adult and Adolescent COVID-19 Patients Presumed to Have Myocarditis**

Reference	Age (yr), Sex	Clinical Presentation	Elevated Troponin or BNP Level	ST-T Changes on ECG	LVEF	Edema or LGE on CMR	Treatment	Outcome
Zeng JH, et al. <sup>12</sup> (2020)	63, M	Fever and pneumonia	Both	No	Reduced	NA	Antiviral, steroidal, and ECMO support	Died
Inciardi RM, et al. <sup>13</sup> (2020)	53, F	Fever and chest pain	Both	Yes	40%	Both	Antiviral, steroidal, and inotropic support	Lived
Kim IC, et al. <sup>14</sup> (2020)	21, F	Fever and pneumonia	Both	Yes	Reduced	Both	NA	NA
Doyen D, et al. <sup>15</sup> (2020)	69, M	Fever and ARDS	Both	Yes	Normal	LGE	Steroid	Lived
Paul JF, et al. <sup>16</sup> (2020)	35, M	Fatigue and chest pain	Yes; NA	No	Normal	LGE	Ramipril and bisoprolol	Lived
Gnecchi M, et al. <sup>17</sup> (2020)	16, M	Fever and chest pain	Yes; NA	Yes	52%	Both	Steroid	Lived
Craver R, et al. <sup>18</sup> (2020)	17, M	Sudden death	—	—	—	—	—	Died*
Hu H, et al. <sup>19</sup> (2021)	37, M	Dyspnea and chest pain	Both	Yes	27%	NA	Coronary angioplasty	Lived
Coyle J, et al. <sup>20</sup> (2020)	57, M	ARDS and shock	Both	Yes	35%	LGE	Steroid and tocilizumab	Lived
Fried JA, et al. <sup>21</sup> (2020)	54, F	Chest pressure	Yes; NA	Yes	30%	NA	IABP and inotropic support	Lived
Tavazzi G, et al. <sup>22</sup> (2020)	69, M	Shock	Both	Yes	25%	NA**	ECMO and inotropic support	Lived

ARDS = acute respiratory disease syndrome; BNP = brain natriuretic peptide; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; F = female; IABP = intra-aortic balloon pump; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; M = male; NA = not available

\* Dead on arrival; autopsy was performed

\*\* Underwent endomyocardial biopsy

from original diagnosis, or the presence of specific heart-related symptoms. Determining whether younger patients would have similar effects warrants research, and the need to investigate the long-term CV consequences of COVID-19 remains.

In a report of 17 French children who had Kawasaki disease (KD) and who were admitted to the intensive care unit (ICU), 14 (82%) had evidence of recent COVID-19 infection, and 13 (76%) had myocarditis.<sup>25</sup> Myocarditis was diagnosed on the basis of laboratory findings of elevated Tn levels and from echocardiograms that showed decreased left ventricular ejection fraction. Two patients with myocarditis had electrocardiographic changes (elongated QT interval and occasional ventricular arrhythmias or diffuse ST-segment elevation). Further studies are needed to confirm whether myocarditis caused by COVID-19 can be diagnosed from histologic analysis or viral genome identification. If there is a direct link between myocardial injury and SARS-CoV-2 infection, targeted treatments and follow-up protocols could be developed.

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### Indirect Effects of COVID-19 on the Heart

Numerous indirect mechanisms appear to contribute to secondary CV involvement in patients who have COVID-19. These factors can cause cardiac injury, exacerbate existing cardiac injury, and lead to death.

Elevated cardiac Tn levels, which can signal or induce myocardial injury,<sup>26</sup> can be found in patients who have severe illnesses, including sepsis and septic shock,<sup>27</sup> and they are associated with higher mortality rates. Experience with COVID-19 patients has been similar.

In a study conducted in China,<sup>28</sup> acute cardiac injury (defined as a high-sensitivity cardiac TnI level >99th percentile upper reference limit) was reported in 32 of 54 patients (59%) who died of COVID-19, but in only one of 137 survivors (<1%;  $P < 0.0001$ ). Shi and colleagues<sup>29</sup> reported a mortality rate of 51.2% in 82 patients who were hospitalized with COVID-19 and who had cardiac injury (defined as elevated high-sensitivity Tn levels). Guo and associates<sup>30</sup> compared mortality rates in patients who had COVID-19 based on the presence of CV disease and whether the TnT level was elevated. In the patients with CV disease, the rate was 69.4% in those with elevated TnT levels and 13.3% in those with normal TnT levels. In the patients without CV disease, the rates were 37.5% and 7.6%, respectively. These study results indicate that elevated Tn levels in patients with COVID-19 are associated with higher mortality rates.

Arentz and coauthors<sup>31</sup> reported that new-onset cardiomyopathy (globally decreased systolic function detected on echocardiograms) developed in 7 of 21 critically ill patients with COVID-19. Stress-induced (takotsubo)

cardiomyopathy, reported in patients with COVID-19, may mimic acute coronary syndrome or sepsis-related cardiomyopathy.<sup>32,33</sup>

Cytokine storm has been described in some patients with COVID-19, as was the case during the SARS outbreak in 2002. Early observations in patients with COVID-19 included similar increases in interleukin (IL)-6 levels, which appear to correlate directly with infection severity and mortality rates.<sup>34</sup> Cytokine storm has been associated with direct myocyte injury and apoptosis, endothelial dysfunction, disruption of coronary plaque, and microthrombogenesis.<sup>35</sup> The downregulation of ACE2 by SARS-CoV-2, with consequent loss of protective CV effects on target organs, may magnify the cytokine storm into an overwhelming inflammatory response.<sup>36</sup> An ongoing clinical trial to test recombinant ACE2 may produce more information on the role of modulating the ACE2 receptor.

Although CV involvement in patients with COVID-19 disease is clearly associated with poor outcomes, it is not clear whether COVID-19 directly causes CV disease or indirectly results from systemic inflammatory syndrome and secondary myocardial injury. Biomarkers (including Tn elevation) and cardiac images help to evaluate the severity of injury.<sup>8</sup> However, they do not differentiate between primary myocarditis and secondary cardiac injuries, such as increased myocardial oxygen demand due to hyperinflammation, ACE2-mediated loss of protective CV effects on target organs, hypoxemia-mediated excessive intracellular calcium leading to cardiac myocyte apoptosis, a microvascular disease with microangiopathy, vasculitis, exacerbation of underlying cardiac disease, impaired renal function (leading to Tn accumulation), and MI types I and II.<sup>8</sup> Troponin elevation in patients with COVID-19 has also been correlated with D-dimer elevation, and autopsies have revealed small-vessel thrombosis and right ventricular dilation.<sup>37</sup> Thus, right ventricular strain and dysfunction secondary to acute cor pulmonale in acute respiratory distress syndrome can also cause Tn and BNP elevation. SARS-CoV-2 infection has also been associated with metabolic dysfunction, myocardial inflammation, and sympathetic nervous system activation, all of which predispose patients to cardiac arrhythmias. According to one report,<sup>38</sup> arrhythmias developed in 23 of 138 patients (16.7%) hospitalized with COVID-19. Arrhythmias were observed in 7% of patients who did not need ICU support and in 44% of patients who did.<sup>39</sup>

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### Cardiac Presentations of COVID-19 in Children

In January 2020, the first report of COVID-19 infection in Chinese children included 6 cases with no mention of cardiac involvement.<sup>40</sup> Likewise, in another

report from China, children presented predominantly with fever and respiratory illness, and no cardiac complications were mentioned.<sup>41</sup> In an initial study of COVID-19 infection in 48 North American children admitted to pediatric ICUs,<sup>42</sup> 83% had serious comorbidities; 73% presented with respiratory symptoms, 38% needed invasive ventilation, and 23% had failure of at least 2 organ systems. These findings confirmed substantial COVID-19 illness in children, but less frequent cardiac involvement than in adults.

Subsequently, a multisystem inflammatory syndrome in children (MIS-C) was observed in an unexpectedly large number of children hospitalized for cardiogenic shock or acute left ventricular dysfunction, most of whom had been exposed to COVID-19. In 35 European children, 80% needed inotropic support, 28% needed mechanical circulatory support with venoarterial extracorporeal membrane oxygenation, and 66% of those with respiratory symptoms needed mechanical ventilation.<sup>43</sup> In the United Kingdom, 58 hospitalized children had a pediatric MIS (similar to MIS-C) potentially associated with COVID-19; symptoms ranged from fever and inflammation to myocardial injury, shock, and development of coronary artery aneurysms.

Presentation and progression overlapped with historical numbers in KD and KD shock syndrome; however, the patients with pediatric MIS were older (median age, 9 yr, vs 2.7 yr in KD and 3.8 yr in KD shock) and had higher levels of inflammatory markers such as C-reactive protein (median, 229 mg/L, vs 67 mg/L in KD and 193 mg/L in KD shock).<sup>44</sup> Similar overlaps and distinctions were found by others.<sup>45</sup> In 21 French children (median age, 7.5 yr; range, 3.7–16.6 yr) who had features of KD, 19 (90%) had evidence of recent COVID-19 infection.<sup>25</sup> Of 186 children in the U.S. who had MIS-C, 135 (73%) were previously healthy, 131 (70%) were positive for COVID-19, and 164 (88%) were hospitalized.<sup>46</sup> Involved organ systems included the gastrointestinal in 171 (92%), CV in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). Coronary artery aneurysm (Z score,  $\geq 2.5$ ) was documented in 8% of patients, and KD-like features in 40%.

The mechanism linking prior COVID-19 exposure to MIS-C is unknown. The relationship between MIS-C and SARS-CoV-2 infection suggests that the pathogenesis involves postinfectious immune dysregulation. In most children with MIS-C, test results are negative for the SARS-CoV-2 antigen but positive for the antibody. Administering anti-inflammatory medications to patients with MIS-C can improve their symptoms, which suggests that the illness is inflammatory and possibly caused by antibody-mediated mechanisms. Moreover, the infection course and immune response in children with MIS-C differ from those in adults in whom severe disease develops, warranting further study.

## Managing Cardiovascular Complications

When patients with COVID-19 present with the usual respiratory conditions and the potential for CV complications, the main goal is to provide supportive care. Cardiac diagnostic imaging such as echocardiography or CMR should be used during initial evaluation or when findings could help to direct management.<sup>47</sup> Hemodynamically stable patients with acute heart failure should undergo guideline-directed medical therapy. Patients with cardiogenic shock may need inotropic agents, vasopressors, and ICU monitoring. If inotropic support fails, intra-aortic balloon pumps should be considered as first-line mechanical circulatory support.<sup>21</sup> European Society of Cardiology guidelines recommend low-dose steroids for adults in the presence of any of 3 conditions: refractory shock, SARS, or mechanical ventilation.<sup>47</sup> Investigators are using convalescent serum and specific antiviral medications to treat patients with COVID-19 who are in cardiogenic shock. In patients with severe COVID-19 and cytokine storm, treating hyperinflammation may decrease the risk of death.<sup>48</sup> In MIS-C, immunomodulation therapies often include intravenous immune globulin, glucocorticoids, and IL-6 inhibitors or IL-1 receptor antagonists.<sup>46</sup> A multidisciplinary team, including intensive care, cardiology, infectious disease, and rheumatology specialists, should monitor patients who have MIS-C—ideally in a pediatric ICU, because clinical deterioration can occur rapidly.

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## Conclusion

Myocardial injury is an essential pathogenic feature of COVID-19, but its mechanisms are not clear. Elevated levels of cardiac biomarkers, chiefly cardiac Tn, indicate acute cardiac injury and are associated with poor outcomes. Continuous inflammation may cause new-onset heart failure and other CV complications, as in other types of viral myocarditis. Endomyocardial biopsy samples may help to differentiate primary viral myocarditis from secondary myocardial dysfunction; however, EMB samples may not confirm myocarditis, so uniform CMR criteria for the diagnosis of SARS-CoV-2 myocarditis are needed. Autopsy findings may eventually enable a better understanding of the pathophysiology of COVID-19 disease and its long-term effects on the heart, thus informing future management.

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