

REVIEW

## COVID-19 and the Heart

### COVID-19 y el corazón

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## ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19) has resulted in a global health crisis. Prior to the arrival of this viral pandemic, the world was already plagued with a significant burden of cardiovascular disease. With the introduction of the novel virus, the world now faces a double jeopardy. Early reports have suggested an increased risk of death in individuals with underlying cardio-metabolic disorders. The exact effects of COVID-19 on the cardiovascular system are not well determined, however lessons from prior viral epidemics suggest that such infections can trigger acute coronary syndromes, arrhythmias and heart failure via direct and indirect mechanisms. In this article, we aimed to discuss the effects and potential underlying mechanisms of COVID -19 as well as potential implications of treatments targeted against this virus on the cardiovascular system.

In December of 2019, a novel coronavirus was identified as the etiology of a number of pneumonia cases complicated with acute respiratory failure in Wuhan, China, eventually spreading across China and throughout the world, and resulting in an unprecedented pandemic with incalculable consequences. The World Health Organization (WHO) designated the disease COVID-19, which stands for coronavirus disease 2019, which in turn, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the Johns Hopkins Coronavirus Resource Center, the case fatality rate of COVID-19 is 6.87% worldwide, 5.22% in the United States, and 4.4.5% in Colombia <sup>1</sup>. However, this high mortality rate is likely influenced by significant underdiagnosis or underreporting of asymptomatic or mildly symptomatic individuals that have not been nor will be tested, and thus, the overall mortality rate is believed to be significantly lower. Moreover, reports from the Chinese Centers for Disease Control have found that the case fatality ratio varies due to location, age, sex, and comorbid conditions. In fact, individuals with existing cardiovascular disease (CVD) as a comorbidity were found to have a 10.5% higher fatality than those who did not <sup>2</sup>. This data indicates that patients with pre-existing CVD were not only more susceptible to the virus, but were also more inclined to sustain critical outcomes and even death. In addition, there is growing evidence that COVID-19 can also manifest with an acute cardiovascular syndrome, even in individuals without pre-existing cardiac conditions.

**Conflict of Interest:**

None declared

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While numerous studies have reported the clinical and epidemiological features of this novel virus, the association between COVID-19 and the cardiovascular system is not fully understood. The difficulty in determining this association may lie in the commonality shared between the two. Pre-existing CVD such as heart failure or coronary artery disease may overlap certain symptomatology experienced with COVID-19. For example, dyspnea, a key feature of heart failure, is also common in individuals with advanced stages of COVID-19 and ultimately gives rise to hypoxemia<sup>3,4</sup>. The resultant hypoxemia may cause atrial fibrillation, an arrhythmia that is known to have a preponderance in elderly individuals, who also happen to be at a higher risk of mortality than younger individuals<sup>2</sup>. While there is limited data with respect to the COVID-19 induced cardiovascular complications, a recently published study by Wang et al. sought to understand acute cardiac injury, which they defined as newly detected abnormalities on echocardiology and electrocardiography or an elevation of troponin I, in COVID-19 patients. The study reported that 7.2% of COVID-19 patients suffered from acute cardiac injury and moreover, that 16.7% of patients experienced arrhythmias<sup>5</sup>. Furthermore, another study conducted by Huang et al. reported an acute cardiac injury rate of 14% in COVID-19 individuals<sup>3</sup>. Wang et al. also reported that 58.3% and 25% of their patients had preexisting comorbidities such as hypertension and heart disease, respectively<sup>5</sup>. As per the report published by the National Health Commission of People's Republic of China (Trial Version 4), the elderly population with coronary heart disease, hypertension, and diabetes were found to be more prone to be afflicted with COVID-19<sup>6</sup>.

Even with scant data available on this topic, it is possible to postulate that patients with underlying cardiovascular comorbidities, once infected with COVID-19, are susceptible to adverse cardiac events. This rationale is reinforced by the idea that COVID-19 is associated with a severe inflammatory response which may trigger ischemia in susceptible individuals with concomitant cardiovascular comorbidities. This inflammatory state, coupled with inflammatory activity already present within a coronary atherosclerotic plaque, may destabilize the plaque and cause it to rupture<sup>7</sup>. There is also evidence suggesting that in the presence of an acute SARS infection, left ventricular dysfunction may occur even among individuals without any preexisting cardiovascular disease, propounding that this ventricular impairment may be due to a biologically driven cytokine storm<sup>8</sup>. The cardinal feature of a cytokine storm is an unchecked, dysfunctional immune response that continually activates and proliferates immune regulatory cells, namely lymphocytes and macrophages. A recently published study reported that COVID-19 patients were found to have higher levels of cytokines in their plasma<sup>3</sup>.

There is also concern for COVID-19 causing myocarditis. Postmortem biopsy analysis of a COVID-19 patient by Xu et al. revealed scarce amounts of mononuclear inflammatory infiltrates in the interstitial space of the patient's myocardium, suggesting that the novel coronavirus may cause myocarditis<sup>9</sup>. However, there is limited data to conclude the temporal association between COVID-19 and myocarditis and this warrants further study. As myocardial biopsies are invasive, we suggest utilizing cardiac magnetic resonance imaging in conjunction with clinical evidence suggestive of acute coronary syndrome documented on electrocardiography as an alternative option in suspected cases as these modalities are more frequently available. Recent studies investigating angiotensin-converting enzyme 2 (ACE2), a receptor that is avidly expressed in the heart, was found to have a strong affinity to bind to COVID-19's Spike protein<sup>10,11</sup>. ACE2 expression is greatly increased in individuals with hypertension and diabetes mellitus as they are managed with ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB), causing an upregulation in ACE2<sup>12,13</sup>. This finding has brought to light the hypothesis that ACE2 may mediate the cardiac injury seen with COVID-19. In light of this theory, a proposal for alternative treatment regimen that does not upregulate ACE2 activity may be beneficial in hypertensive COVID-19 individuals. Interestingly, a recent multicenter observational study in 1128 hospitalized COVID-19 patients with hypertension found in a propensity score-matched analysis that those who were taking ACEI or ARB had a lower risk of all-cause mortality compared with ACEI/ARB non-users (adjusted HR, 0.37; 95% CI, 0.15-0.89; P = 0.03)<sup>14</sup>. Obviously, more

studies, including large-scale prospective cohort studies and randomized controlled trials, are needed to better understand the association between ACEI/ARB and survival in COVID-19. In the mean time, the American Heart Association, American College of Cardiology, and Heart Failure Society of America recommend that ACEI and ARBs be continued in COVID-19 patients as per current guidelines.

There is extensive research being conducted to develop antiviral medications and vaccines in an attempt to control the virus. Of these, Remdesivir and hydroxychloroquine are promising medications that have proven to be effective in inhibiting the virus *in vitro*<sup>15</sup>. Remdesivir, an RNA dependent RNA polymerase inhibitor with broad-spectrum antiviral efficacy, is currently undergoing testing in both mild to moderate as well as severe cases of COVID-19. Hydroxychloroquine, a drug known commonly for its antimalarial properties, has been studied by Gautret et al.; they reported in 26 patients that took hydroxychloroquine at a daily dose of 600 mg had a significant viral load reduction (measured in nasopharyngeal swab cultures) at 6 days post-inclusion compared to 16 control patients<sup>16</sup>. In the same study, when hydroxychloroquine was combined with azithromycin, an antibacterial administered for superimposed infections as a result of the virus, the viral elimination was quicker and more effective<sup>16</sup>. There has also been attention drawn to the dual combination of lopinavir and ritonavir. In an open-label trial of 199 hospitalized patients who tested positive for COVID-19 and had low oxygen saturation indices underwent a 14-day course of lopinavir and ritonavir. In comparison to standard care, the study established that the dual drug therapy did not significantly diminish viral loads, hasten clinical improvement, or reduce 28-day mortality<sup>17</sup>. These are clearly preliminary findings from small observational studies. Larger, well-designed, including randomized clinical trials will be required to investigate the true impact of these drugs on COVID-19 outcomes.

This is particular relevant to hydroxychloroquine and azithromycin, drugs that are known to cause certain adverse effects, specifically in a cardiovascular context<sup>18</sup>. QT prolongation is one such side effect that has been associated with these drugs and is known to lead to the development of polymorphic ventricular tachycardia, termed torsades de pointes (TdP). Although it may be self-limiting, it has the potential to cause death. Risk factors for QT interval prolongation and TdP include increased age, female sex, comorbid conditions (e.g., liver disease or heart failure), and electrolyte abnormalities (e.g., hypomagnesemia, hypokalemia, and hypocalcemia). QT prolongation occurs due to changes in intracellular ion channels. Inhibition of the rapid component of the delayed rectifier outward potassium channels causes a delay in the action potential<sup>19</sup>. While there are slight variations in the definition of a prolonged QT interval, a corrected QT interval (QTc) of >500 milliseconds is considered abnormal for both men and women. We suggest that all patients with suspected COVID-19 should have a baseline electrocardiogram performed on admission to document baseline QTc interval, especially prior to administering these drugs. If the QTc subsequently increases to  $\geq 500$  milliseconds or if the change in QT interval is  $\geq 60$  milliseconds from the baseline ECG, the risk versus benefit of continued treatment with the QT-prolonging medication should be reassessed, with consideration of dose adjustment and/or additional interventions, including correction of all electrolyte abnormalities, discontinuation of other non-essential QT-prolonging medications, and placement on continuous telemetry. Management of patients with TdP who are hemodynamically stable is possible with discontinuation of the offending medication or correction of the underlying disturbance (electrolyte abnormalities), with some scenarios necessitating treatment with intravenous magnesium. Hemodynamically unstable patients require more aggressive management such as advanced cardiac life support protocols.

Important lessons from previous coronavirus epidemics tells us that viral infections have the ability to trigger arrhythmias, acute coronary syndromes, and exacerbate underlying heart conditions such as heart failure<sup>20-22</sup>. COVID-19 is proving to be very similar to its

predecessors. It is capable of both exacerbating preexisting cardiac disease and inducing new cardiovascular pathology. The extent, severity, and clinical implications of COVID-19's effects on the cardiovascular system, as well as the efficacy of proposed treatments are not fully known, and must be studied in greater detail throughout the course of this rapidly evolving pandemic.

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