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REVIEW ARTICLE

Possible Long-Term Cardiovascular Effects of COVID-19

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Abstract: Coronavirus Disease 2019 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a worldwide pandemic. Since 2019, the virus has mutated into multiple variants that have made it harder to eradicate and have increased the rate of infection. This virus can affect the structure and the function of the heart and can lead to cardiovascular symptoms that can have long-lasting effects despite recovery from COVID-19. These symptoms include chest pain, palpitations, fatigue, shortness of breath, rapid heartbeat, arrhythmias, cough and hypotension. These symptoms may persist due to myocardial injury, cardiac inflammation or systemic damage that may have been caused during infection. If these symptoms persist, the patient should visit their cardiologist for diagnosis and treatment plan for any type of cardiovascular disease that may have developed Post-COVID 19.

Keywords: SARS-CoV-2, COVID-19, cardiovascular effects, cardiovascular, long-term, cardiology.

1. INTRODUCTION

SARS-CoV-2 is the virus that caused the novel disease COVID-19, which emerged in late 2019.As of October 11, 2021, COVID-19 has affected over 200 countries where there has been a total of 237,383,711 cases worldwide and a total of 4.8 million fatalities [1]. COVID-19 is spread primarily by saliva droplets, coughing or sneezing from an infected person. Common symptoms include fever, chills, cough, shortness of breath, fatigue, muscle aches, headaches, loss of sense of smell and taste, vomiting and diarrhea [2]. Serious complications of COVID-19 include acute respiratory failure, pneumonia, acute respiratory distress syndrome, acute liver injury, acute cardiac injury, septic shock, disseminated intravascular coagulation, multisystem inflammatory syndrome, chronic fatigue, rhabdomyolysis and myocardial infarction [3].

People with preexisting cardiovascular diseases such as uncontrolled hypertension, arrhythmias, deep venous thrombosis, congestive heart failure, cardiomyopathy and myocarditis have a 4-fold higher risk of death [4]. Renin-angiotensin-aldosterone may play a role in the pathogenesis of a COVID-19 infection [5]. There have been some concerns that the pandemic has affected the availability of acute cardiovascular care, which may indirectly contribute to excess mortality in patients affected [6].

Coronaviruses are enveloped, single-stranded RNA viruses and can be divided into four genera such as α, β, γ, and δ [7]. SARS-CoV (Middle East respiratory syndrome coronavirus) and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) are both classified under the β coronaviruses [8]. Over time, viruses constantly change through mutations and new variants are expected. These variants are important to identify since they differ in pathogenicity, infectivity, transmissibility and antigenicity. There are currently 4 different variants identified in the United States-alpha, beta, gamma, and delta [9]. The alpha variant, from SARS-Cov-2 B.1.1.7, was first identified in South Eastern England in September 2020. This variant is known to be 1.5 times more transmissible, and the risk of death is 1.6 times higher than previous variants [10]. The beta variant, from SARS-Cov-2 B.1.351, first identified in South Africa, has the ability to re-infect people who have already had been infected previously with COVID-19 and has shown to be resistant to a few vaccines [11]. The gamma variant produced from SARS-Cov-2 P.1, first identified in Brazil, is known to spread faster than other variants and has shown that specific monoclonal antibody treatments are less effective against this variant. The fourth variant, delta, produced

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by SARS-Cov-2 B.1.617.2, was first identified in India [12]. As of August 26, 2021, the Centers for Disease Control and Prevention have classified the delta variant to be twice more contagious than the other variants and may cause more severe illness [13].

With an increase of variants, there is an increase in COVID-19 cases and faster infectivity, resulting in a strain on healthcare resources. Furthermore, this can also lead to more hospitalizations, ultimately increasing a country's mortality rate [14]. Although some immune responses driven by current vaccines may be less effective against specific variants, vaccinations do offer a percentage of protection against most variants. The current COVID-19 vaccinations authorized by the United States Food and Drug Administration still offer significant protection against variants and may help prevent serious illness [15].

2. PATHOPHYSIOLOGY

There are three different pathways *via* which SARS-CoV-2 can affect the heart such as direct myocardial injury, indirect myocardial injury, or hypoxia secondary to respiratory failure. In direct myocardial injury, the spike protein of SARS-CoV-2 fuses to angiotensin-converting enzyme-2 receptors that are present in the lung, heart, ileum, kidney and bladder. Once the virus attaches, this leads to myocardial infarction. Angiotensin-converting enzyme-2 dependent myocardial infarction leads to the decreased angiotensin-converting enzyme-2 expression [16]. The infection causes macrophage infiltration in the heart leading to myocarditis [17]. In severe cases, myocarditis can lead to blood clots, abnormal heartbeat, heart failure and sudden death [18]. Healthy, young people are at a greater risk of developing fatal heart complications with the delta COVID-19 variant. A study done in the United States focused on COVID-19-associated cardiac problems and found that 14,000 people between the ages of 12 and 17 developed heart inflammation from COVID-19 [19].

Indirect myocardial injury is another mechanism that causes damage to the heart. It can be caused by different mechanisms that activate T-helper cells type 1 and 2 that release cytokines. Direct and indirect myocardial injury can lead to impairment of intracellular calcium transport and signal transduction through B-adrenergic receptors that can affect the myocardial contractile function. Signs of myocardial injury can be seen with elevated cardiac troponin markers, abnormal ECG findings and magnetic resonance-based imaging (Fig. **1**) [16, 20].

Hypoxia can occur due to microvascular causes, such as hypercoagulability [16]. Lack of oxygen can lead to increased pulmonary vasoconstriction in an attempt to redistribute pulmonary blood flow from regions of low PO2 to high oxygen availability. Thus, chronic pulmonary vasoconstriction can result in pulmonary hypertension that will increase afterload on the right ventricle, resulting in heart failure [21]. Severe infections can not only cause hypoxia but also can predispose the patient to thrombotic events [22]. One of the major risk factors in acquiring COVID-19 is pre-existing cardiovascular disease [23]. Pre-existing cardiovascular diseases may include arrhythmias, myocarditis, acute coronary syndrome, left ventricular systolic dysfunction, reverse Takotsubo syndrome and heart failure [24-26]. In a study with 416 hospitalized patients, there were 19.7% patients who had cardiac injury. This study also showed that 40% of confirmed COVID-19 patients who were hospitalized had a history of cardiovascular disease [27]. Patients with an underlying cardiovascular condition have a greater progression of the disease that can become critical. This progression can happen due to heightened coagulation function, pro-inflammatory effects, increased viscosity during febrile illnesses, and endothelial dysfunction. This can ultimately lead to heart failure [28, 29]. In a study of 191 hospitalized patients in Wuhan, China, 23% of infected COVID-19 patients died of heart failure [30].

Notable mutations in variants have altered the biochemistry of the spike proteins present in the SARS-CoV-2 virus. It affects the transmission rate of the virus. It has been seen in the alpha mutation that presents two deletions of amino acids H69/V70. This deletion has made this virus twice as infectious [31, 32]. Another mutation called N501 present in Alpha, Gamma, and Beta has made the virus more infective [33]. These variants can cause severe disease, evade diagnostic tests or resist antiviral treatment [34].

Current vaccines are great for providing immunological protection against the SARS-CoV-2 virus. These vaccines were designed for initial strains and are still recommended for new mutants even if the effectiveness for the mutants is lowered [35]. Booster vaccines are recommended to be taken after a person is vaccinated to provide additional protection against mutated forms of the virus [36]. In rare instances, myocarditis and pericarditis have been associated with COVID-19 vaccinations. The Centers for Disease Control and Prevention have reported 4.8 cases out of 1 million, mostly young males, with myocarditis after the 2nd vaccination. On another rare occasion, pericarditis can be seen in older patients who have received vaccines [37].

3. SIGNS AND SYMPTOMS OF CARDIOVASCULAR INJURY

Symptoms from myocardial injury include cough, fever, myalgia, headache, dyspnea, palpitations, chest pain, hypotension, cardiogenic shock, and heart attack (Fig. **1**) [38, 39]. Cardiovascular injury may be asymptomatic in patients, so it is essential to check for cardiac troponin elevation, asymptomatic cardiac arrhythmias, N-terminal pro-brain natriuretic peptide levels and cardiac imaging (Fig. **1**) [40]. Coronavirus can increase the risk of ST-segment elevation myocardial infarction. (STEMI) [41]. COVID-positive patients have a 36% risk of a primary outcome of in-hospital death, stroke, recurrent myocardial infarction, or repeat revascularization. COVID-positive patients with STEMI have an increased risk of a high thrombus burden. ST elevation can occur due to arrhythmias and hypoxia [42, 43].

In a Spanish study, 139 healthcare workers who were diagnosed with COVID-19 underwent an ECG study 10 weeks after diagnosis. It was noted that 40% of the cases had pericarditis, and 11% had myocarditis, and some participants were presented with some degree of pericarditis coexisting with myocardial inflammation (Fig. **1**). Some of these patients will then be at risk for subsequent arrhythmias. In a study by the Centers for Disease Control and Prevention in

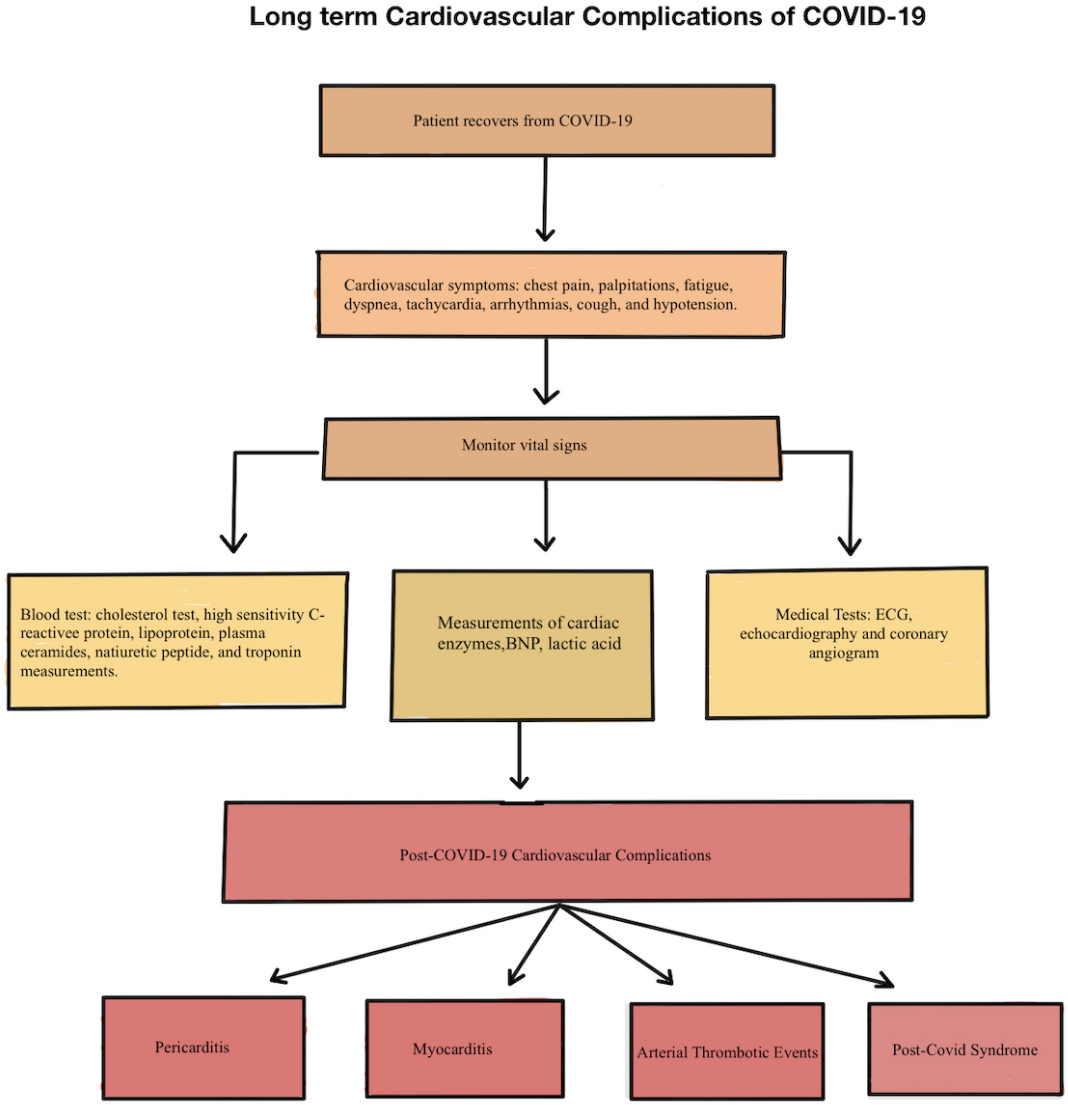

Fig. (1). Long term cardiovascular complications such as pericarditis, myocarditis, arterial thrombotic events and post-COVID Syndrome may develop after a person recovers from COVID-19. After initial recovery, cardiovascular symptoms may develop in which a patient should visit a cardiologist for any abnormalities in blood tests, measurements of cardiac enzymes BNP, lactic acid and medical tests [38, 39, 44-48].

July 2020, a third of the people tested claimed that they had not returned to their normal state of health two to three weeks after testing positive [44]. There is also growing evidence of an association between post-COVID-19 patients and arterial thrombotic events (Fig. **1**). There is evidence that COVID -19 can lead to increased viscosity of blood that can lead to venous thromboembolic events. Symptoms that these patients can present with are swelling, leg pain, chest pain, numbness or weakness [45]. Post COVID -19 Syndrome may present with symptoms such as fatigue, shortness of breath, cough, joint pain, chest pain, cognitive difficulties, difficulty concentrating, depression, muscle pain, headache, rapid heartbeat, and intermittent fever (Fig. **1**). These symptoms are most likely from systemic damage of the organs post-COVID, grief, loss and post-traumatic stress disorder after treatment in the intensive care unit [46]. There is still ongoing research on long-term damage to lungs, heart, immune system, brain and other organs [44].

4. TREATMENT

Patients with persisting symptoms post COVID-19 such as chest pain, fatigue, dyspnea, and heart palpitations should visit their cardiologist four weeks after initial diagnosis to be assessed for any cardiovascular complications. Testing such as ECG, echocardiography, diagnostic tests, and laboratory tests may be required to check for cardiac biomarkers to assess cardiac function (Fig. **1**) [47, 48]. Afterwards, the cardiologist will come up with a personalized care plan and introduce cardiac treatment [49]. Patients diagnosed with pericarditis may be prescribed corticosteroids or colchicine to treat the inflammation. Additionally, they may benefit from over-the-counter medications such as Advil or Motrin to relieve the pain [50]. For people diagnosed with myocarditis, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers may be prescribed to lower blood pressure, beta blockers to improve arrhythmias and remodeling, diuretics to

decrease fluid congestion, and corticosteroids to reduce inflammation [51]. Treatment for arterial thrombosis may include embolectomy, thrombolytic injection, angioplasty, or coronary artery bypass graft. Medical therapy may include statins to lower cholesterol, drugs to reduce blood pressure such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, anticoagulants and antiplatelets to reduce blood clotting [52]. There is currently ongoing research to treat the overall symptoms of people who suffer from Post-COVID-19 Syndrome, one of them being a new drug called Leronlimab. This drug is currently being tested in new trials targeting patients who still have symptoms after being diagnosed with COVID-19. It is a double-blinded trial that has been approved by the Food and Drug Administration. There is still insufficient evidence to suggest its efficacy for this syndrome [53].

CONCLUSION

Long-term cardiovascular effects of COVID-19 include pericarditis, myocarditis, coexisting pericarditis with myocarditis, arterial thrombosis, and post-COVID-19 syndrome. These conditions leave patients previously diagnosed with COVID-19 with long-termsymptoms such as fatigue, breathlessness, and chest pain. The cause of these symptoms may be due to cardiac myocyte damage of the heart, cardiac inflammation, formation of clots, worsening of pre-existing cardiovascular conditions or systemic problems that have occurred during the initial COVID-19 infection. There are still many unknown reasons as to why some of these symptoms may persist after treatment. The current treatment of these symptoms would be to visit a cardiologist, undergo cardiac evaluation, and go through a care plan with a cardiologist. Depending on the diagnosis, medications such as anticoagulants, blood pressure lowering drugs, or corticosteroids may be utilized. There are still new medications that are up for a trial, with an emphasis on long-lasting symptoms Post-COVID 19.

LIST OF ABBREVIATIONS

SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2
STEMI	=	ST-segment elevation myocardial infarction

CONSENT FOR PUBLICATION

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