

COVID-19: cardiovascular manifestations—a review of the cardiac effects

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The coronavirus first reported in China in November 2002 in the form of atypical pneumonia known as the severe acute respiratory syndrome (SARS).^[1] The virus then appeared in 2012 in Saudi Arabia as the Middle East respiratory syndrome (MERS).^[2] The year 2020 witnessed a novel β -coronavirus related to the previous detected viruses.^[3] It was the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) — a positive single stranded RNA virus. It was suspected that bats were the main reservoir, leading to speculation about possible animal to human transmission.^[4,5] The ongoing COVID-19 pandemic caused by SARS-CoV-2 has already infected over 450 million people worldwide and has killed more than 6 millions. The pandemic strained the emergency medical services in many countries and led to an increased mortality.^[6] Researchers stated that the virus can spread from large respiratory droplets on contaminated surfaces, aerosol transmission of small respiratory droplets and from symptomatic, asymptomatic and pre-symptomatic patients.^[7] The WHO declared the COVID-19 as a pandemic on March 11, 2020.^[8] Coronaviruses are named after the spikes on their surface which form a crownlike dome, and they are known to cause respiratory infections in humans and animals.^[9] SARS-CoV-2, in particular, clinical pattern progresses from an early infection (Stage I), pulmonary phase (Stage II) to hyperinflammation (Stage III) and can be lethal.^[10] This has created multiple challenges since acute respiratory infections are one of the known triggers for cardiovascular diseases (CVD),^[11] and the presence of CVD may complicate and worsen the course of the infectious dis-

ease.^[12] COVID-19 binds via its spike protein the Spike protein receptor-binding domain to the zinc peptidase angiotensin-converting enzyme 2 (ACE2), which acts as a receptor for the virus.^[13] ACE2 is a surface molecule found on vascular endothelial cells, arterial smooth muscle, and cardiac myocytes.^[14,15] When COVID-19 attaches to ACE2 receptors on myocardial cells, it causes their down regulation as well as imbalance of Angiotensin II (AII) and Angiotensin 1-7 (A1-7) which is generated by ACE2; unbalanced AII activity leads to endothelial injury, inflammation exacerbation and known thrombotic consequences seen in COVID-19 in addition to the inflammatory pathways provoked by lung viral invasion.^[16–19]

It is well established that COVID-19 has many systemic and respiratory manifestations, including major severe cardiovascular consequences. COVID-19 has been shown to cause myocarditis, type 1 myocardial infarction (acute coronary syndrome and spontaneous coronary artery dissection), type 2 myocardial infarction, arrhythmias, micro-angiopathy, disseminated intravascular coagulation, systemic infection and cytokine storm.^[20–27]

COVID-19 COAGULATION DISORDERS AND BLEEDING

Studies have shown a link between SARS-CoV-2 and coagulopathy; however, the coagulopathy is distinct from that associated with sepsis associated disseminated intravascular coagulation (DIC) in that D-dimer levels are elevated, while platelet, fibrinogen and PT levels are normal.^[28] Increased risk

of death has been observed in coagulopathy associated with COVID-19.^[29-42]

CARDIAC MANIFESTATIONS IN COVID-19

Different mechanisms are involved in the pathogenesis of cardiac injury: microthrombosis is common and may persist even after clearing the virus, Myocarditis is usually very limited in extent while direct myocardial injury by the virus is not common. The immune response in COVID-19 infection is divided into two phases. The first occurs during the incubation stage of the disease, during which the adaptive immune system works to eliminate the virus; if for any reason, a defect occur at this stage, COVID-19 will disseminate and induce systemic organ damage, with more significant destruction of organs with higher expression of ACE2 receptors, including lung, endothelial cells, the heart, and the kidneys. This massive damage leads to phase 2: severe inflammation in the affected organs, which in case of heart damage, can lead to myocarditis with severely reduced ejection fraction.^[43] Cardiac troponin I levels were significantly higher in those with severe COVID-19-related symptoms compared with those with non-severe presentation.^[44] Myocardial injury, present in 19.7% of COVID-19 patients, was associated with higher levels of inflammatory biomarkers, more severe pulmonary involvement, higher need for non-invasive and invasive ventilation and increased rates of acute respiratory distress syndrome, acute kidney injury, and coagulation disorders.^[45] Patients with myocardial injury were at higher risk of death.

COVID-19-induced cardiac injury is also via hyper-stimulation of the immune system/cytokine storm, which can lead to vascular endothelial injury as well as cardiac myocyte damage.^[46] Interleukin (IL)-2, IL-10, IL-6, IL-8, and tumor necrosis factor (TNF) are among the proinflammatory cytokines that are considerably increased in severe cases. Such uncontrolled immune system can lead to severe inflammation expressed by worsening preexisting plaques or promote accelerated atherogenesis.^[47] Because of this intense release of potent inflammatory cytokines, catecholamine surge, and microvascular injury, COVID-19 might cause stress

cardiomyopathy (Takotsubo) and increases the vulnerability of preexisting plaques to rupture, leading to acute coronary syndrome.^[48]

COVID-19 AND ACUTE CORONARY SYNDROME

Several recent studies have reported the occurrence of Acute Coronary Syndromes in COVID-19 despite absence of demonstrable obstructive Coronary disease. In 28 Italian patients with ST-elevation myocardial infarction (STEMI) and COVID-19, Stefanini, *et al.*^[49] reported that STEMI represented the first clinical manifestation of COVID-19 in the majority of cases (85.7%) with increased observed mortality was 39.3%. In these patients, coronary angiography revealed the absence of obstructive coronary artery disease (CAD) in 39.3% of cases, a finding also reported by Bangalore, *et al.*^[50] who found non-obstructive disease in one-third of the patients who underwent coronary angiography. In this latter series, the prognosis of STEMI presentation was worse than in the previous report, with a 72% rate of in-hospital mortality. Microvascular thrombosis has also been hypothesized as a mechanism underlying certain cases mimicking presentation of STEMI without obstructive CAD, attributable to endothelial dysfunction and hypercoagulable state associated with COVID-19. Microvascular thrombosis was further investigated by Pellegrini, *et al.*^[51] who analyzed autopsies of 40 hearts from hospitalized patients who died due to COVID in Bergamo, Italy. They found that 14 hearts out of 40 had evidence of myocyte necrosis, mainly in the left ventricle. Nine out of these 14 hearts had microthrombi in myocardial arteries and capillaries. In comparison to intramyocardial thromboembolic material from COVID-19-negative patients with STEMI and aspirated thrombi from COVID-19 patients with STEMI during percutaneous cardiac intervention, microthrombi showed substantially more fibrin and terminal complement C5b-9 immunostaining.^[51]

COVID-19 AND ARRHYTHMIAS

In addition to COVID-19, there are more than 20 viruses that have been linked to myocardial inflammation and myocarditis, with parvovirus B19, hu-



man herpesvirus 6, adenovirus, and coxsackievirus B3 being the most frequent.^[52] The interaction between host variables and viral features is one of the suggested pathways for arrhythmogenicity in viral infections.^[53] Aberrant conduction is caused by altered intercellular coupling, interstitial edema, and cardiac fibrosis, as well as abnormal Ca^{2+} handling and down regulation of K^+ channels, which causes repolarization and action potential conduction problems.^[54] According to Gaaloul, *et al.*,^[52] viral infection causes cardiac inflammation, which results in ion channel malfunction or electrophysiological and structural remodeling as a reason for arrhythmia. In case of COVID-19, arrhythmias could be secondary to hypoxia and pulmonary disease, medication side effects,^[55] direct oxidized Ca^{2+} /calmodulin-dependent protein kinase II activity,^[56] activated protein kinase C, and myocarditis. One of the most prevalent arrhythmias found in COVID-19 patients is sinus bradycardia, which can last up to two weeks.^[57] Other atrial and ventricular arrhythmias, including malignant arrhythmias like ventricular fibrillation and ventricular tachycardia, have been seen in individuals who had no previous history of arrhythmia and were not on QT-prolonging medicines.^[58]

A survey organized by the Heart Rhythm Society showed that common arrhythmias in hospitalized patients with COVID are atrial fibrillation (21%), atrial flutter (5.4%), atrial tachycardia (3.5%), and paroxysmal supraventricular tachycardia (5.7%).^[59] Ventricular arrhythmias were also reported, the most common form was monomorphic premature ventricular contractions (5.3%). Regarding bradycardias in COVID-19 patients, sinus bradycardia and complete heart block were the most reported (8%) and (8%) respectively. First- or second-degree AV block, bundle branch block or intraventricular conduction delay were also reported.^[59] Guo, *et al.*^[58] showed that patients with underlying CVD exhibited elevated levels of troponin-T (TnT), which led to more frequent development of complications including malignant arrhythmias and ventricular tachycardia/fibrillation. Cardiac arrhythmias were two-fold more frequent at elevated Troponin levels.^[58]

In an Italian study, the rate of out-of-hospital cardiac arrests during the first 40 days of the COVID-19 epidemic was compared to the same period a

year earlier.^[60] It was found out that there was a 58 percent rise in out-of-hospital cardiac arrests (362 arrests compared to 229 arrests in the previous year) throughout the research period, which was linked to the incidence of COVID-19. Out of all 362 cardiac arrests, COVID-19 was detected or suspected in 28% of the cases.^[60]

Furthermore, numerous medications used to treat COVID-19 infection, such as azithromycin and hydroxychloroquine, have been shown to cause arrhythmias. These medicines can raise the risk of arrhythmias including torsades de pointes and ventricular tachycardia secondary to prolongation of the QT interval.^[60]

COVID-19 AND HEART FAILURE

The occurrence of Heart failure in the context of COVID-19 infection is well recognized and is multifactorial. It can be the result of a direct effect of the virus on the myocardium or indirectly caused by supply and demand mismatch ischemia, volume overload, cytokine release, stress, renal failure, or overwhelming critical illness.^[61] COVID-19-induced acute coronary syndromes might lead to cardiac failure or aggravate pre-existing conditions.

COVID-19 patients may develop right-sided heart failure as a result of pulmonary involvement, hypoxia and acute respiratory distress syndrome. Right ventricular dilatation was found in 31% of intubated COVID-19 patients in a group of 105 patients hospitalized to Mount Sinai Morningside Hospital (New York, New York).^[24] Right ventricular hypokinesia was seen in 66% of COVID-19 patients with right ventricular enlargement vs. 5% of COVID-19 patients without right ventricular enlargement.^[62]

Bieber, *et al.*^[63] found that left ventricular dysfunction (both systolic and diastolic) and systolic right ventricular dysfunction occurred in 56 percent of their cohort (116 patients) and were more common in individuals with elevated troponin (88.8% vs. 14.3%, $P < 0.001$). Furthermore, this consequence occurs in the absence of a preexisting history of cardiovascular illness, indicating that COVID-19 has a direct role in the pathogenesis of heart failure.^[64] In COVID-19 patients, heart failure with preserved ejection fraction (HFpEF) is a frequent finding in terms of left ventricular dysfunction.^[65]



This finding might be explained by having a preexisting subclinical HFpEF or new diastolic dysfunction induced by systemic inflammation and hypoxia. Furthermore, HFpEF and COVID-19 appear to have a number of cardiometabolic risk factors in common, including obesity and older age.^[66] In the case of severe viral invasion, COVID-19 myocarditis can present as a cardiogenic shock. In a case report by Purdy, *et al.*,^[67] they describe two patients, previously healthy, presenting with cardiogenic shock secondary to prolonged course of COVID. The two patients required treatment with steroids, inotropes, and diuretics before fully recovering 6 to 10 weeks later. One should also keep in mind that in the context of severe inflammatory response and cytokine storm, COVID-19 can present as distributive shock as well.

Biomarkers such as CRP, D dimers and troponin correlate with severity and mortality rates of COVID-19 related complications. A study conducted by Smilowitz, *et al.*^[68] involving 3 281 consecutive adults hospitalized with COVID-19 showed that 2895 patients (88.2%) had measurements of all three biomarkers while only 196 patients (6.8%) had no elevated biomarkers.

COVID-19 VACCINE AND CARDIAC SIDE EFFECTS

A few cardiac manifestations have been attributed to COVID-19 vaccine. In a large study which assessed the cardiovascular adverse effects of COVID-19 vaccines from the WHO database, it was found that several vaccines are associated with cardiovascular adverse events. They include but are not limited to: hypertension, hypotension, palpitations, tachycardia, atrial fibrillation and flutter, angina pectoris, myocardial infarction and cardiac arrest.^[69] Although they remain rare compared to risk of developing such side effects from the infection itself, some unfortunate incidences were encountered following COVID-19 mRNA vaccination including myocarditis and STEMI.^[70,71,72]

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