Review Article

How COVID-19 Can Damage the Heart? – Association of Cardiac Injury with COVID-19: A Narrative Review

Catarina Gregório[1], Daniel Caldeira[1,2,3], Joana Brito[1], Rui Plácido[1], Fausto J. Pinto[1]

[1]Department of Cardiology, Santa Maria Hospital, CHULN, CAML, CCUL@RISE, Faculty of Medicine, University of Lisbon, Lisbon, Portugal, [2]Evidence-Based Medicine Center (CEMBE), Faculty of Medicine, University of Lisbon (Faculdade de Medicina, Universidade de Lisboa), Lisbon, Portugal, [3]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Abstract

Severe acute respiratory syndrome coronavirus 2 and its resulting disease, COVID-19, remain a significant public health concern. Cardiovascular injury is the second most common complication, following respiratory disease, encompassing conditions such as myocarditis, acute myocardial injury, acute coronary syndrome, arrhythmia, and heart failure. It presents with high-troponin levels, reduced left ventricular systolic function, and/or electrocardiographic abnormalities. Cardiac involvement is an independent risk factor for worse clinical outcomes and higher mortality, particularly in the elderly patients. The debate continues regarding whether the cardiac manifestations of COVID-19 result from direct viral infection or indirect cellular injuries. The virus attaches directly to angiotensin-converting enzyme 2 receptor, which is extensively expressed in the heart, invades myocardial tissue, and triggers an excessive inflammatory response. Indirect mechanisms stem from endothelial damage, hypercoagulability and micro-thrombosis, cytokine storm, respiratory failure and hypoxia, and autoimmunity. The pathophysiology of cardiac injury in COVID-19 patients is important to frame the main pathways and biomarkers to encourage new therapeutic trials to improve the disease prognosis and to understand the course of the disease.

Keywords: Angiotensin-converting enzyme 2 receptor, COVID-19, cytokine storm, hypercoagulability, myocardial injury, pathophysiological mechanisms

Introduction

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] and has triggered a global pandemic in 2019.[2] Until July 2023, over 767 million confirmed cases and about 6.9 million deaths have been reported worldwide.[3] While severe respiratory failure is typically regarded as the primary cause of death, COVID-19 also affects the cardiovascular system, leading to frequent cardiovascular symptoms such as chest pain and dyspnea.[1,4]

Acute myocardial injury is the most common extrapulmonary organ complication among critically ill patients[5] and can be present in 5%–37% of individuals hospitalized with COVID-19.[6] This condition is more prevalent in patients with preexisting cardiovascular disease (CVD) compared to those without CVD (54.5% versus 13.2%, respectively),[7] in elderly patients, and in those with comorbidities such as diabetes, hypertension, obesity, and chronic lung disease.[2]

Cardiac injury is commonly defined in most studies as an increase in high-sensitivity cardiac troponin above the 99th percentile of its upper reference limit[2] or as elevated levels of other biomarkers such as brain natriuretic peptide,[8] creatine kinase, and D-dimer.[9] It should be noted that some definitions may also include evidence of new electrocardiographic or echocardiographic abnormalities.[6]

In COVID-HEART, a prospective study that included 342 in-hospital individuals with elevated troponin levels,

Received: 06-08-2023; **Accepted:** 07-02-2024; **Published:** 09-05-2024

Access this article online

Quick Response Code:

Website: journals.lww.com/hhmi

DOI: 10.4103/hm.HM-D-23-00035

Address for correspondence: Prof. Fausto J. Pinto, Department of Cardiology, Santa Maria Hospital – CHULN, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal.
E-mail: faustopinto@medicina.ulisboa.pt

How to cite this article: Gregório C, Caldeira D, Brito J, Plácido R, Pinto FJ. How COVID-19 can damage the heart? – Association of cardiac injury with COVID-19: A narrative review. Heart Mind 0;0:0.

61% of the patients presented left or right ventricular systolic dysfunction, myocardial scar (with an ischemic or micro-thrombotic pattern), or pericardial effusion as determined by cardiac magnetic resonance imaging.[10] In fact, some of the primary cardiovascular manifestations of COVID-19 include myocarditis, heart failure, stress cardiomyopathy, arrhythmias (especially atrial arrhythmias[2]), acute coronary syndrome (ACS) and myocardial infarction (both type 1 and 2), Kawasaki disease, thromboembolic events (stroke, pulmonary emboli, and deep-vein thrombosis), cardiogenic shock, and cardiac arrest.[7,11,12]

Among COVID-19 patients who present with ST-elevation myocardial infarction (STEMI), those who are infected have a higher likelihood of experiencing multivessel coronary thrombosis, stent thrombosis, and an increased need for additional treatments such as glycoprotein IIb/IIIa inhibitor agents, aspiration thrombectomy, and multivessel percutaneous coronary intervention.[13] Venous thromboembolism (VTE) is quite common in hospitalized COVID-19 patients, with some studies reporting a prevalence as high as 17%.[13] New-onset left heart failure is relatively rare, while right heart failure is frequently observed in critically ill COVID-19 patients due to a combination of factors, including lung injury, pulmonary thromboembolism, and pulmonary hypertension.[13,14] Myocarditis is a well-documented manifestation, especially in young and healthy patients, with nonspecific symptoms that can delay the diagnosis.[14,15] Atrial fibrillation is the most frequently reported arrhythmia in severe cases, with an estimated prevalence of 13% in patients without a previous history of this condition.[16]

Among the pandemic, when the health-care system was overwhelmed, the accessibility of health-care facilities for patients with cardiovascular conditions had become compromised, which could be considered as an additional contributor to adverse cardiovascular outcomes during this challenging period. A multicenter retrospective study involving 16,117 patients diagnosed with ACS revealed a notable reduction of over 20% in the weekly count of ACS hospitalizations (95% confidence interval [CI] [1.6, 35.4], $P = 0.04$), as well as a decrease in the proportion of patients undergoing invasive therapeutic strategies. The total ischemic time experienced a rise of 22.7 min ($P = 0.02$), and mechanical complications became more prevalent during the pandemic compared to the prepandemic period (1.98% versus 0.98%; $P = 0.006$).[17]

Acute cardiac injury in these patients has been linked to higher morbidity and mortality,[8] a worse prognosis, and an increased need for mechanical ventilation compared to patients without cardiac involvement (46.3% versus 3.9%).[18] Remarkably, 11.8% of deceased COVID-19 individuals without preexisting heart disease exhibited significant heart damage. Its prevalence can be up to 13 times higher in intensive care inpatients than in nonintensive care individuals.[19] Nevertheless, the precise mechanism of myocardial injury caused by SARS-CoV-2 remains unclear.

This review will focus on potential mechanisms that explain myocardial injury in COVID-19, including direct viral invasion or indirect cellular injuries (immune-mediated with a pro-inflammatory state, hypercoagulability, systemic hypoxia, and autoimmunity) [Figure 1].[8,20]

Direct Myocardial Injury: Angiotensin-Converting Enzyme-2 Tropism

SARS-CoV-2 enters the human cells by attaching to a specific receptor called angiotensin-converting enzyme-2 (ACE2), a type 1 transmembrane protein, which is located on the surface of host cells. This attachment is facilitated by a viral envelope protein known as the spike glycoprotein, which has two functional subunits.[1] While the S1 subunit exhibits an affinity for the receptor and assists in viral attachment to the target cell, the S2 subunit is responsible for viral fusion with the cell membrane.[21] Following its binding to ACE2, the spike protein undergoes proteolytic activation by cellular proteases, including the transmembrane protease serine 2. This activation enables the virus to invade target cells through an endosome-dependent mechanism, facilitating its subsequent replication.[7,21] Inside the host cell, SARS-CoV-2 utilizes the cell's machinery to synthesize viral proteins and replicate its genetic material.[22]

Furthermore, ACE2 has the capacity to enzymatically convert angiotensin II into angiotensin-(1–7) and also metabolize angiotensin I (Ang I), resulting in the production of angiotensin-(1–9), which promotes vasodilation and exerts anti-inflammatory, antioxidant, and cardioprotective effects.[1,23] Their expression is downregulated by SARS-CoV-2. Hence, there is an increase in the level of angiotensin II leading to endothelial dysfunction, chronic myocardial hypoxia, and cardiomyocyte death.[21]

ACE2 is highly expressed in alveolar tissue and cardiomyocytes but also in epicardial adipocytes, pericytes, fibroblasts, endothelial cells, and smooth muscle cells.[1,24,25] Some *in vitro* studies suggest that the heart is inherently susceptible to SARS-CoV-2 infection. Sharma *et al.* demonstrated that the virus can infect human-induced pluripotent stem cell-derived cardiomyocytes through ACE2- and cathepsin-mediated mechanisms, ultimately resulting in virus-induced apoptosis within 72 h.[26] Another study, which established an engineered heart tissue model to mimic COVID-19 myocardial pathology, confirmed the virus's affinity for ACE2 receptors on cardiomyocytes. Upon analyzing the infected cells, researchers observed an upregulation of genes associated with immune cell activation (including chemokines and cytokines), stress-induced transcription, and responses to viral pathogens. Otherwise, genes related to muscle contraction (such as troponin, actin, and myosin chain), metabolism (including glycerol-3-phosphate dehydrogenase and pyruvate dehydrogenase), and mitochondrial function (such as mitochondrial cytochrome C oxidase) were found to be downregulated, which may explain the compromise in

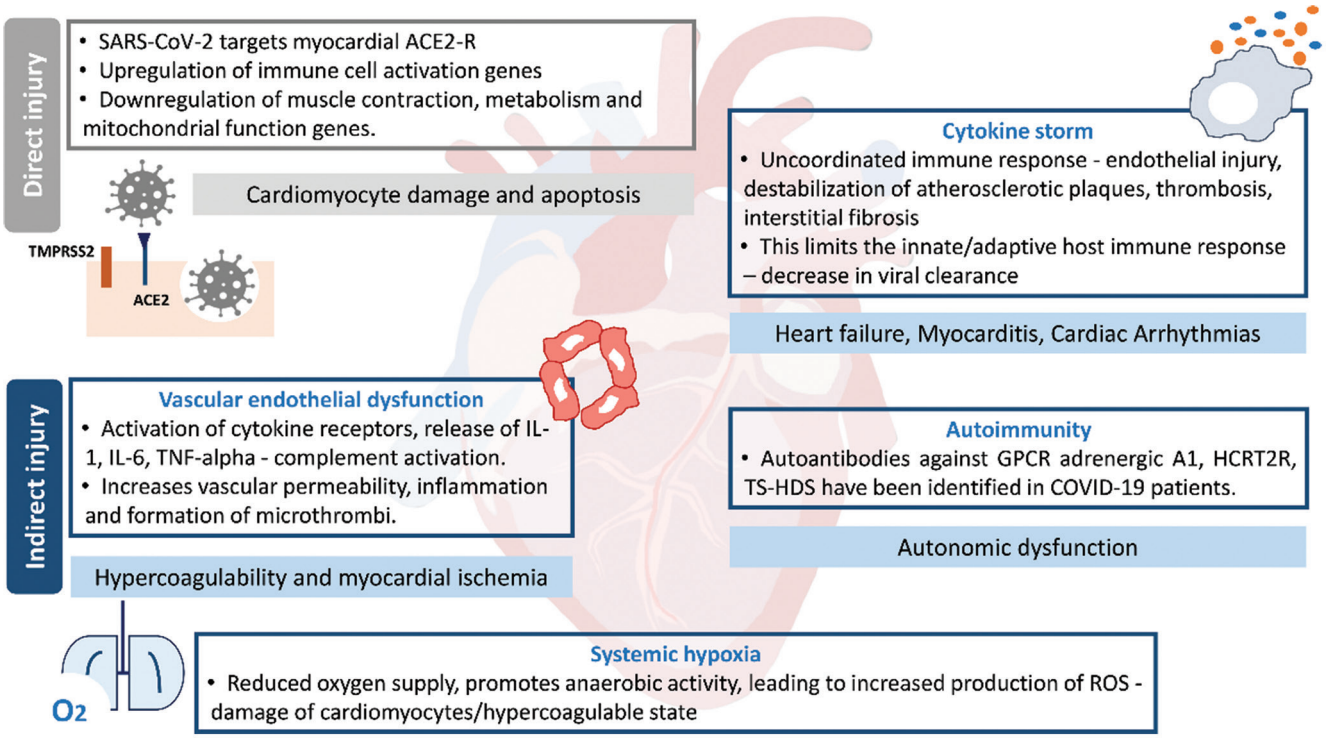

Figure 1: The proposed mechanism(s) of COVID-19-associated myocardial injury. SARS-CoV-2=Severe acute respiratory syndrome coronavirus 2, ACE2-R=Angiotensin converting enzyme 2-receptor, TMPRSS2=Transmembrane serine protease 2, ACE2=Angiotensin converting enzyme 2, IL=Interleukin, TNF=Tumor Necrosis Factor, GPCR adrenergic A1=G protein coupled adrenergic A1 receptors, HCRT2R=Orexin receptors, TS-HDS=Trisulfated heparin disaccharide, ROS=Reactive oxygen species, O_2=Oxygen

contractile function of cardiomyocytes,[27] with evidence of sarcomere loss occurring approximately 3 days after SARS-CoV-2 inoculation.[4]

Bailey *et al*. detected viral proteins and single-stranded ribonucleic acid (RNA) from SARS-CoV-2 nucleocapsids in the myocardium and inflammatory cells within the areas of myocardial cell injury.[27] Viral RNA was found in low quantities, with a focal and patchy distribution, within the cytoplasm and perinuclear regions of cardiomyocytes and the interstitium.[9] Some other population-based studies also support the hypothesis of direct myocardial injury. Sakamoto *et al.* identified viral RNA using the real-time polymerase chain reaction in the left atrium of just one out of 15 hearts from deceased COVID-19 patients.[28] In another postmortem autopsy study, Ferrer-Gómez *et al*. found genetic viral material in only one out of the 30 hearts analyzed.[29] However, in the review by Roshdy *et al*., 47% of the studied hearts were positive for SARS-CoV-2.[30] These discrepancies in results could be attributed to variations in laboratory techniques and the stage of disease progression/duration of illness.[29]

In addition to cardiomyocytes, other studies have confirmed that SARS-CoV-2 infects adipocytes located within the visceral epicardium and infiltrates adipocytes within the myocardium (cells that express high levels of the ACE2 receptor in murine models). This phenomenon, besides the adipose tissue serving as a reservoir of pro-inflammatory cytokines, may explain the heightened risk and severity of COVID-19 in obese patients.[2,9,31]

All these studies emphasize a mechanism involving direct myocardial injury mediated by ACE2, which could potentially serve as a therapeutic target.

At the beginning of the pandemic, concerns about the safety of renin-angiotensin system inhibitors were raised, provided that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) had the capacity to upregulate the ACE2 receptor and potentially increased susceptibility to SARS-CoV-2. However, there are no human studies supporting this.[32] Actually, many population-based studies proved that exposure to ACEIs/ARBs did not increase the risk of adverse clinical outcomes, including a severe course of the disease and all-cause mortality among COVID-19 patients,[33] and currently, available data do not support routinely discontinuing of this therapy in noncritically ill COVID-19 patients if there is an indication for treatment.[34-36] One of these studies, the BRACE CORONA study, a multicenter randomized controlled trial, evaluated the impact of discontinuation compared to continuation treatment with ACEIs/ARBs, in patients with mild-to-moderate COVID-19 who were taking medication before hospital admission and found that there was no significant difference in the mean number of days alive and out of the hospital at 30 days.[37]

Small *in vitro* studies also proposed the hypothesis that ACEIs play a significant role in counterbalancing proinflammatory responses, promoting an up-regulation in the expression of the Interleukin-1 Receptor Type 2 and RETN gene (inhibitors of proinflammatory cytokines) in monocytes of these patients.[38]

Finally, two clinical trials tested the effectiveness of two experimental intravenous renin-angiotensin system agents – TXA-127 (a synthetic angiotensin [1–7]) and TRV-027 (a specific angiotensin II type 1 receptor-targeted drug), in patients with severe COVID-19 and new-onset low oxygen levels, but they were not effective.[39]

Indirect Myocardial Injury: Endothelial Dysfunction and Hypercoagulability

In addition to SARS-CoV-2's tropism for ACE2-expressing cells, another target for infection is the vascular endothelium. Healthy endothelial cells express the factors that promote vascular relaxation, inhibit platelet activation and aggregation, and promote fibrinolysis.[40] Endothelial dysfunction, on the other hand, results in the overproduction of thrombin and the formation of microthrombi, improves inflammation, increases coronary capillary permeability, and decreases myocardial perfusion due to vasospasm.[1,2,19] The majority of cardiovascular risk factors are associated with endothelial dysfunction, which may explain a more severe disease course and higher mortality of COVID-19 patients with cardiovascular comorbidities.[1]

The virus can directly infect the endothelial cells or activate the renin-angiotensin system through the angiotensin II type 1 receptor, promoting a profound systemic inflammatory response. Both of these processes lead to an increase in reactive oxygen species and activate the nuclear factor kappa B (NF-κB). NF-κB, in turn, inactivates nitric oxide (NO), converting it into peroxynitrite and reducing its production by uncoupling endothelial NO synthase.[1,40] The disruption of the balance between vasoconstriction and dilatation affects organ perfusion and promotes myocardial ischemia.[4]

SARS-CoV-2 infection has been shown to elicit the activation of numerous cytokine receptors, thereby inducing the release of pro-inflammatory cytokines, notably interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-alpha), which promote complement activation with subsequent endothelial cell dysfunction,[41] compromising the integrity of the endothelial barrier, resulting in heightened vascular permeability. In addition, it exposes the underlying collagen, thereby fostering the formation of blood clots.[20] Cytokines may also initiate platelet activation and aggregation, thereby potentiating a hypercoagulable state.[42]

In fact, it is estimated that over than 20% of COVID-19 patients may experience abnormal coagulation, as evidenced by elevated D-dimer levels and thrombocytopenia.[43] The prevalence of this phenomenon may be even more significant, as some autopsy studies have identified deep-venous thrombosis in 58% of patients in whom VTE was not suspected before death. This figure is notably higher than the reported incidence in other viruses, like H1N1 influenza.[4]

Besides venous events, it has been suggested that microthrombosis may represent one of the mechanisms behind arterial events.[2,4] In a postmortem investigation, Bois *et al*. identified nonocclusive microthrombi in the small intramyocardial vasculature in 80% of COVID-19 patients.[42] Pellegrini *et al.* conducted a pathological analysis of 40 cardiac specimens obtained from hospitalized COVID-19 patients who succumbed to the disease in Italy, in February 2020, and microthrombi was the primary contributor to myocyte necrosis, occurring in 35% of the patients, predominantly in the left ventricle. Remarkably, in 64% of these instances, the microthrombi exhibited a higher degree of fibrin and C5b-9 complement deposition when compared to COVID-19-negative individuals. Furthermore, electrocardiograms indicated ischemic abnormalities in 20% of the study's population and in almost half of the clinically symptomatic patients (STEMI or stroke). Notably, focal myocardial necrosis was most frequently observed in the inferior and lateral walls of the left ventricle and in the ventricular septum, mirroring the distribution pattern of microthrombi. There is no difference in the percentage of cases with viral RNA detected in myocardial tissue, irrespective of the presence of myocardial necrosis (14.3% versus 23.1%, $P = 0.51$). Therefore, these investigators suggest that direct viral invasion may not play a singular role in the development of myocardial necrosis.[44]

Hanson *et al*. assessed 21 consecutive cases of heart autopsy decedents, between April and December 2020, and compared their findings to the cases of virus-associated heart failure (such as influenza B, coxsackie virus B3, adenovirus 2, and hepatitis C virus). Thrombi were found in both macro and microvasculature in 19.1% of these patients, a discovery supported by a significant elevation of CD61, a marker of platelet activation, in these individuals. In addition, arterial and venous thrombi were more frequently observed in the hearts of COVID-19 patients,[9] as evidenced by an increase in fibrinogen and von Willebrand factor – factors associated with coagulopathy – in individuals with SARS-CoV-2 infection.[9,45]

At the onset of the pandemic, most experts recommended pharmacologic VTE prophylaxis for all hospitalized COVID-19 patients, with the possibility of extending it to a postdischarge phase in high-risk patients.[32] Recently, in the COVID-19 treatment guidelines of the National Institutes of Health, the expert panel does not recommend the use of prophylactic anticoagulation in nonhospitalized patients. For hospitalized patients without evidence of VTE, the guidelines recommend the use of a therapeutic dose of heparin for patients with D-dimer levels above the upper limit of normal who require low-flow oxygen and do not require intensive care unit level care and the use of a prophylactic dose of heparin as VTE prophylaxis for individuals who require intensive care unit-level care, including those receiving high-flow oxygen.[46-48]

Indirect Myocardial Injury: Cytokine Storm

A cytokine storm is an intense and aggressive immune response characterized by the excessive production of pro-inflammatory cytokines and other chemical mediators.[41] It is well known that cytokines, as a part of the innate and adaptive immune response, are the first line against viral infections.[4,12] In COVID-19, an excessive and uncoordinated immune response that results in the overproduction of cytokines leads to organ damage, through endothelial injury, destabilization of atherosclerotic plaques, and the formation of blood clots (thrombosis).[12,49] Several studies have associated the elevated levels of IL-6, IL-8, and ferritin with the prediction of an unfavorable clinical course and higher mortality rates.[7,43] Guo *et al*. demonstrated a significant positive linear correlation between plasma troponin T-levels and high-sensitivity C-reactive protein levels in 187 confirmed COVID-19 patients, emphasizing the critical role of inflammation in cardiac injury.[50]

One of the triggers for cytokine storm is the increased levels of angiotensin II (a proinflammatory mediator involved in the inflammatory response in several pathological processes[51]) in the bloodstream due to the virus's ACE2 tropism,[41] as previously mentioned.

Many cytokines seem to be involved. In an autopsy study, elevated levels of intercellular adhesion molecule-1 (ICAM-1), IL-1β, IL-6, matrix metalloproteinase-9 (MMP-9), and TNF-alpha were found in six hearts from COVID-19 patients. These cytokines are considered key players in the inflammatory response.[52] In fact, MMP-9 recruits T-helper type 2 cells that release cytokines (IL-4 and TGF-beta) causing myocardial fibrosis,[52] which is supported by an increase in collagen type 1 and 3 in the interstitial and perivascular space.[41] Furthermore, the presence of neutrophils and macrophages can trigger fibroblast activation, leading to cardiac remodeling and interstitial fibrosis, which may contribute to the development of heart failure.[9]

IL-6 and ICAM-1 are often found in activated endothelial cells.[9,52] When endothelial cells are activated, they become more permeable to blood plasma proteins and release pro-inflammatory cytokines and adhesion molecules. These molecules help recruit white blood cells and trigger a cascade of signaling events that release NF-κB. This limits the innate and adaptive host immune responses, further decreasing viral clearance and resulting in the propagation of the disease.[2,53]

Other cytokines appear to be involved, including IL-2, IL-7, interferon-γ, interferon-gamma-induced protein 10, chemokine ligand-10, monocyte chemoattractant protein-1, and chemokine ligand 2,[54] particularly in patients who experience acute heart failure and myocarditis.[4] Some of these pro-inflammatory cytokines may contribute to vascular inflammation,[54] which can impair coronary blood flow and oxygen supply.[41] Mast cells, abundant in histamine, are also involved and contribute to heightened capillary permeability, microvascular leakage, and the subsequent onset of myocardial interstitial edema.[1]

The systemic inflammatory response syndrome accelerates the development of new coronary plaques by activating lipid-laden foam cells and destabilizing preexisting ones. This process involves the expression of macrophages and adhesion molecules on leukocytes, as well as increased shear stress, which leads to plaque rupture and thrombus formation.[12,55] This can result in either STEMI or non-STEMI.[7] In addition, the influx of CD4 T-cells promotes heightened cytokine production, stimulating smooth muscle cells to migrate to the intima and produce collagen and other fibrous components.[10] The cytokine storm also triggers the generation of reactive oxygen species and free radicals, inducing oxidative stress. This oxidative stress further depletes NAD + and adenosine triphosphate (ATP), ultimately leading to apoptosis and necrosis of cardiomyocytes.[56]

The interstitial myocardial edema appears to be one of the mechanisms that explains arrhythmias in patients with myocarditis, due to the disarrangement of the syncytium's structure.[57] It has also been found in postmortem myocardial biopsies of COVID-19 patients, which may account for the high prevalence of cardiac arrhythmias in these patients.[52] In addition, three inflammatory markers, IL-6, TNF-alpha, and IL-1, have been shown to prolong the ventricular action potential by activating the hERG potassium channel, potentially leading to ventricular arrhythmias in severely ill COVID-19 patients.[21,58]

Stress cardiomyopathy has been documented during the COVID-19 pandemic, and the cytokine storm has been proposed as a potential mechanism, with emotional stress, respiratory infections, and hospitalization being considered as potential triggers.[59]

Indirect Myocardial Injury: Systemic Hypoxia

One of the primary manifestations of SARS-CoV-2 is hypoxemia, which predominantly affects organs with high oxygen and energy requirements.[14] In the lungs, the virus induces necrosis and the infiltration of inflammatory cells, increases airway resistance, promotes mucus secretion, and reduces the production of alveolar surface-active substances. These effects collectively contribute to respiratory failure. Concurrently, viral infection often accompanies fever, elevated heart rate, and increased cardiac output. This results in a significant rise in myocardial oxygen demand while potentially reducing oxygen supply, leading to a likelihood of subendocardial ischemia.[53,59]

Hypoxia decreases ATP hydrolysis, reducing the energy supply for cell metabolism and promoting anaerobic activity, which in turn increases the production of reactive oxygen species and may damage the cellular membrane.[1,53] Furthermore, this oxidative stress encourages a hypercoagulable state and amplifies the inflammatory response.[7]

Hypoxia also disrupts calcium channel activity, leading to an increase in calcium influx into the cell. This, in turn,

damages cardiomyocytes, promotes apoptosis, and exacerbates cardiovascular dysfunction in COVID-19 patients.[11] All of these mechanisms, along with the adrenergic response triggered by viral infection, and resulting vasoconstriction, exacerbate ischemia.[7]

Considering the high prevalence of myocardial injury in COVID-19 patients with preexisting CVD, it is conceivable that the infection may unmask type 2 myocardial infarction in patients with stable coronary artery disease.[59]

Indirect Myocardial Injury: Autoimmunity

Autonomic dysfunction has been reported as a sequela in long COVID,[60] with labile blood pressure, episodes of hypertension, and orthostatic hypotension being the most commonly reported events.[60,61] The pathophysiology of dysautonomia following COVID-19 is largely speculative and is based on small studies. One of the proposed mechanisms suggests direct virus-induced damage via hematogenous or transneuronal routes.[60] Autoimmunity is another explanation.

In fact, patients with long COVID-19 have high levels of autoantibodies against G-protein-coupled adrenergic A1 receptors, which are involved in neurotransmission and regulation of the sympathetic nervous system by binding and activating neurotransmitters like norepinephrine. Norepinephrine is a diagnostic marker of postural orthostatic tachycardia syndrome.[62,63] Another study identified the presence of autoantibodies against orexin receptors in the hypothalamus. These receptors mediate arousal and the stress response while also regulating arterial blood pressure and cardiovascular reflexes.[62]

Novak *et al.* evaluated nine patients with postacute sequelae of COVID-19 and found high levels of trisulfated heparin disaccharide (TS-HDS) antibodies in 44% of these patients.[64] TS-HDS is located in peripheral nerves and has been identified as a marker of small fiber neuropathy in previous studies.[65] In their study, 78% of patients exhibited small fiber neuropathy, which raised the hypothesis that the high titers of TS-HDS antibody could explain dysautonomia.[64]

Large-scale studies are crucial for obtaining a comprehensive understanding of the role of autoimmunity in this disease, particularly its long-term effects, and for exploring immunotherapy as a potential therapeutic intervention to mitigate the symptoms.

Association of Other Viruses and Cardiovascular Diseases

Numerous viruses are linked to the onset or exacerbation of cardiovascular diseases

SARS-CoV-1 is one of the seven coronaviruses known to infect humans. It caused an outbreak in 2002, infecting approximately 8,000 patients worldwide and resulting in about 774 deaths, nearly 10% mortality.[66,67] This virus uses the same mechanism of SARS-CoV-2 to enter the cardiovascular system (by binding the ACE2 receptors).[68] Both viruses promote an inflammatory response and a cytokine storm, however, they exhibit variances in the types of cytokines involved, with SARS-CoV-1 infection resulting in the activation of a smaller array of cytokines compared to SARS-CoV-2 infection, which may explain less pathogenicity and risk of adverse cardiovascular outcomes.[68]

A small population-based study analyzed 121 patients diagnosed with SARS-CoV-1, of whom 20.1% had cardiovascular risk factors and found that 10.7% of patients exhibited transient cardiomegaly without symptoms of heart failure. Only one patient, with severe pneumonia, presented a transitory decrease in left ventricular ejection fraction on echocardiogram and received inotropic support by intravenous dobutamine, with a total recovery of cardiac function at follow-up. Concerning cardiovascular symptoms during the hospitalization period, tachycardia was observed in 71.9% of individuals, making it the most common sign, followed by hypotension (50.4%) and bradycardia (14.9%).[67] There are some other references in the literature regarding cardiac damage in SARS-CoV-1 patients. A subclinical diastolic impairment on echocardiogram was also documented by Li *et al.,* in a prospective study with 46 patients.[69] One small postmortem study reported pulmonary thromboembolism, deep-vein thrombosis, and occlusive coronary artery as findings in patients with documented SARS-CoV-1 infection.[70]

Middle East Respiratory Syndrome coronavirus (MERS-CoV) was first identified in 2012 and it primarily presents as an acute respiratory illness with rapidly progressive pneumonia and a case-fatality rate of 34.3%.[71,72] The MERS-CoV uses another cellular receptor-dipeptidyl peptidase 4 (CD26), which is expressed in various lung cells but also in the kidney, small intestine, liver, and prostate.[73] Relevant reports indicate that these patients have a high proportion of cardiovascular comorbidities, such as hypertension, which was present in 30.3% of individuals (95% CI, 18.3%–42.2%), cardiac disease in 20.9% (95% CI, 10.7%–31.1%), and diabetes mellitus in 45.4% (95% CI, 27.3%–63.5%), when compared to other coronaviruses.[71] Some case reports and case series have documented myocarditis and pericarditis as cardiac manifestations in individuals with MERS-CoV infection. In a case report, one patient with elevated troponin-I levels and symptoms of acute-onset heart failure in the first 24 h of admission was found to have myocarditis on cardiac magnetic resonance with a linear sub-epicardial pattern of late gadolinium enhancement in inferior and lateral walls of the left ventricle. A severe impairment of left ventricle systolic function remains after 3 months.[74]

The prevalence of cardiac damage in COVID-19 compared to previous coronavirus outbreaks is a subject of debate due to limited and heterogeneous data from the small-scale studies.[15,75]

Influence of COVID-19 vaccination on cardiac complications

COVID-19 vaccines have been associated with limited cardiac complications, such as myocarditis and pericarditis,

especially among young adults. These complications are thought to arise from the activation of both innate and adaptive immune responses and an autoimmune-mediated mechanism. Myocarditis is more commonly associated with the second vaccine dose compared to the first or third doses.[76] However, among the subgroup of patients most affected with vaccine-induced cardiac injury (aged 12–17 years), the risk of adverse cardiac outcomes was 1.8–5.6 times higher following SARS-CoV-2 infection than after receiving the second vaccine dose.[77]

One of the complications of COVID-19 is the risk of cardiovascular events, including acute myocardial infarction. In a population-based study, Jiang *et al*. analyzed the data from the National COVID Cohort Collaborative (N3C), which included an extensive group of patients in the United States who had contracted SARS-CoV-2. This cohort comprised a total of 1,934,249 vaccine-eligible individuals, with 10.1% having received full vaccination. Their study demonstrated that both full vaccination (adjusted hazard ratio [aHR] of 0.59; 95% CI: 0.55–0.63) and partial vaccination (aHR of 0.76; 95% CI: 0.65–0.89), using either mRNA or viral vector vaccines, were associated with a reduced risk of major adverse cardiovascular events following a SARS-CoV-2 infection, with a mean follow-up time of 180 days after viral infection.[78] Another retrospective cohort study, involving patients from Korea, revealed that full COVID-19 vaccination (with two doses) was linked to a decreased likelihood of experiencing acute myocardial infarction and ischemic stroke following a COVID-19 infection.[77]

Furthermore, the COVID-19 vaccine has been shown to be protective for patients with preexisting CVD. Gupta *et al.* analyzed a total of 1,578 subjects with a STEMI who were registered in the North India STEMI (NORIN-STEMI) registry from August 2021 to August 2022. After a 30-day follow-up period, all-cause mortality was observed in 201 patients, accounting for 12.7% of the total. The adjusted odds of mortality were markedly lower in the vaccinated group (adjusted odds ratio [aOR]: 0.58, 95% CI: 0.47–0.71) at 30 days but also during the 6-month follow-up period (aOR: 0.54, 95% CI: 0.44–0.65) in comparison to the nonvaccinated group.[76]

Therefore, the World Health Organization, and various medical societies, including the American Heart Association and the European Society of Cardiology, endorse the COVID-19 vaccination for individuals with cardiac disease.[32,79,80]

Conclusion

Myocardial injury in SARS-CoV-2 infection is a multifactorial phenomenon in which direct and indirect mechanisms may contribute to cardiovascular damage. The most widely accepted mechanisms include direct viral invasion, dysregulated immune responses, hypoxemia resulting from respiratory failure, and infarction secondary to thrombosis. A comprehensive understanding of the pathophysiology of cardiac damage is of the utmost importance for the early recognition and disease diagnosis, as well as for the development of more effective drug interventions.

Author contributions

Catarina Gregório designed the study and wrote the first draft of the manuscript with Daniel Caldeira, Joana Brito, Rui Plácido, and Fausto J Pinto. Each co-author contributed to either the delivery of the study or helped with the writing. All authors have given final approval for the current version to be published.

Ethical statement

Ethical statement is not applicable for this article.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

Nil.

Conflicts of interest

Dr. Fausto J. Pinto is an Editorial Board Member of *Heart and Mind*. Dr. Daniel Caldeira is an Early Career Editorial Board Member of *Heart and Mind*. The article was subject to the journal's standard procedures, with peer review handled independently of Dr. Fausto J. Pinto and the research groups. There are no conflicts of interest.

References

1. Bing Y, Yalin W, Xiaosu S, Gaizhen L, Fengqin W, Fenfang Z, *et al.* Possible mechanisms of SARS-CoV2-mediated myocardial injury. CVIA 2023;8:19.
2. Li S, Wang J, Yan Y, Zhang Z, Gong W, Nie S. Clinical characterization and possible pathological mechanism of acute myocardial injury in COVID-19. Front Cardiovasc Med 2022;9:862571.
3. World Health Organization. COVID-19 Weekly Epidemiological Update, Edition 150, 6 July 2023. World Health Organization; 2023.
4. Siripanthong B, Asatryan B, Hanff TC, Chatha SR, Khanji MY, Ricci F, *et al.* The pathogenesis and long-term consequences of COVID-19 cardiac injury. JACC Basic Transl Sci 2022;7:294-308.
5. Artico J, Shiwani H, Moon JC, Gorecka M, McCann GP, Roditi G, *et al.* Myocardial involvement after hospitalization for COVID-19 complicated by troponin elevation: A prospective, multicenter, observational study. Circulation 2023;147:364-74.
6. Kyriakoulis K, Kyriakoulis I, Trontzas I, Syrigos N, Kyprianou IA, Fyta E, *et al.* Cardiac injury in COVID-19: A systematic review of relevant meta-analyses. Rev Cardiovasc Med 2022;23:404.
7. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, *et al.* Cardiovascular manifestations and treatment considerations in COVID-19. Heart 2020;106:1132-41.
8. Mitrani RD, Dabas N, Goldberger JJ. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. Heart Rhythm 2020;17:1984-90.
9. Hanson PJ, Liu-Fei F, Ng C, Minato TA, Lai C, Hossain AR, *et al.* Characterization of COVID-19-associated cardiac injury: Evidence for a multifactorial disease in an autopsy cohort. Lab Invest 2022;102:814-25.
10. Stuber M, Baggish AL. Acute myocardial injury in the COVID-HEART study: Emphasizing scars while reassuring scares. Circulation 2023;147:375-7.
11. Guan W, Ni Z, Hu Y, Liang WH, Ou CQ, He JX, *et al.* Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.

12. Sheth AR, Grewal US, Patel HP, Thakkar S, Garikipati S, Gaddam J, *et al.* Possible mechanisms responsible for acute coronary events in COVID-19. Med Hypotheses 2020;143:110125.
13. Louis DW, Saad M, Vijayakumar S, Ilyas S, Kokkirala A, Aronow HD. The cardiovascular manifestations of COVID-19. Cardiol Clin 2022;40:277-85.
14. Giacca M, Shah A. The pathological maelstrom of COVID-19 and cardiovascular disease. Nat Cardiovasc Res 2022;1:200-10.
15. The Task Force for the Management of COVID-19 of the European Society of Cardiology, Baigent C, Windecker S, Andreini D, Arbelo E, Barbato E, Bartorelli AL, *et al*. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: Part 1 – Epidemiology, pathophysiology, and diagnosis. Cardiovasc Res 2022;118:1385-412.
16. Lavelle MP, Desai AD, Wan EY. Arrhythmias in the COVID-19 patient. Heart Rhythm O2 2022;3:8-14.
17. Araiza-Garaygordobil D, Montalto C, Martinez-Amezcua P, Cabello-Lopez A, Gopar-Nieto R, Alabrese R, *et al.* Impact of the COVID-19 pandemic on hospitalizations for acute coronary syndromes: A multinational study. QJM 2021;114:642-7.
18. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802-10.
19. Tajbakhsh A, Gheibi Hayat SM, Taghizadeh H, Akbari A, Inabadi M, Savardashtaki A, *et al.* COVID-19 and cardiac injury: Clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. Expert Rev Anti Infect Ther 2021;19:345-57.
20. Friedrich MG, Cooper LT. What we (don't) know about myocardial injury after COVID-19. Eur Heart J 2021;42:1879-82.
21. Yang J, Petitjean SJ, Koehler M, Zhang Q, Dumitru AC, Chen W, *et al.* Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. Nat Commun 2020;11:4541.
22. Dimitrov DS. Virus entry: Molecular mechanisms and biomedical applications. Nat Rev Microbiol 2004;2:109-22.
23. Chung MK, Karnik S, Saef J, Bergmann C, Barnard J, Lederman MM, *et al.* SARS-CoV-2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy. EBioMedicine 2020;58:102907.
24. Lee CY, Huang CH, Rastegari E, Rengganaten V, Liu PC, Tsai PH, *et al.* Tumor necrosis factor-alpha exacerbates viral entry in SARS-CoV2-infected iPSC-derived cardiomyocytes. Int J Mol Sci 2021;22:9869.
25. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res 2020;116:1097-100.
26. Sharma A, Garcia G Jr., Wang Y, Plummer JT, Morizono K, Arumugaswami V, *et al.* Human iPSC-derived cardiomyocytes are susceptible to SARS-CoV-2 Infection. Cell Rep Med 2020;1:100052.
27. Bailey AL, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, *et al.* SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. JACC Basic Transl Sci 2021;6:331-45.
28. Sakamoto A, Kawakami R, Kawai K, Gianatti A, Pellegrini D, Kutys R, *et al.* ACE2 (angiotensin-converting enzyme 2) and TMPRSS2 (transmembrane serine protease 2) expression and localization of SARS-CoV-2 infection in the human heart. Arterioscler Thromb Vasc Biol 2021;41:542-4.
29. Ferrer-Gómez A, Pian-Arias H, Carretero-Barrio I, Navarro-Cantero A, Pestaña D, de Pablo R, *et al.* Late cardiac pathology in severe COVID-19. A postmortem series of 30 patients. Front Cardiovasc Med 2021;8:748396.
30. Roshdy A, Zaher S, Fayed H, Coghlan JG. COVID-19 and the heart: A systematic review of cardiac autopsies. Front Cardiovasc Med 2020;7:626975.
31. Gupte M, Boustany-Kari CM, Bharadwaj K, Police S, Thatcher S, Gong MC, *et al.* ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. Am J Physiol Regul Integr Comp Physiol 2008;295:R781-8.
32. Task Force for the Management of COVID-19 of the European Society of Cardiology. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: Part 2-care pathways, treatment, and follow-up. Eur Heart J 2022;43:1059-103.
33. Caldeira D, Alves M, Gouveia E Melo R, Silvério António P, Cunha N, Nunes-Ferreira A, *et al.* Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers and the risk of COVID-19 infection or severe disease: Systematic review and meta-analysis. Int J Cardiol Heart Vasc 2020;31:100627.
34. Sharma A, Elharram M, Afilalo J, Flannery A, Afilalo M, Tselios C, *et al.* A randomized controlled trial of renin-angiotensin-aldosterone system inhibitor management in patients admitted in hospital with COVID-19. Am Heart J 2022;247:76-89.
35. Baral R, Tsampasian V, Debski M, Moran B, Garg P, Clark A, *et al.* Association between renin-angiotensin-aldosterone system inhibitors and clinical outcomes in patients with COVID-19: A systematic review and meta-analysis. JAMA Netw Open 2021;4:e213594.
36. Cohen JB, Hanff TC, William P, Sweitzer N, Rosado-Santander NR, Medina C, *et al.* Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: A prospective, randomised, open-label trial. Lancet Respir Med 2021;9:275-84.
37. Lopes RD, Macedo AV, de Barros E Silva PG, Moll-Bernardes RJ, Dos Santos TM, Mazza L, *et al.* Effect of discontinuing versus continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A randomized clinical trial. JAMA 2021;325:254-64.
38. Duvvuri VR, Baumgartner A, Molani S, Hernandez PV, Yuan D, Roper RT, *et al.* Angiotensin-converting enzyme (ACE) inhibitors may moderate COVID-19 hyperinflammatory response: An observational study with deep immunophenotyping. Health Data Sci 2022;2022:1-14.
39. Self WH, Shotwell MS, Gibbs KW, de Wit M, Files DC, Harkins M, *et al.* Renin-angiotensin system modulation with synthetic angiotensin (1-7) and angiotensin II Type 1 receptor-biased ligand in adults with COVID-19: Two randomized clinical trials. JAMA 2023;329:1170-82.
40. Nägele MP, Haubner B, Tanner FC, Ruschitzka F, Flammer AJ. Endothelial dysfunction in COVID-19: Current findings and therapeutic implications. Atherosclerosis 2020;314:58-62.
41. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, *et al.* COVID-19 infection: An overview on cytokine storm and related interventions. Virol J 2022;19:92.
42. Bois MC, Boire NA, Layman AJ, Aubry MC, Alexander MP, Roden AC, *et al.* COVID-19-associated nonocclusive fibrin microthrombi in the heart. Circulation 2021;143:230-43.
43. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
44. Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, *et al.* Microthrombi as a major cause of cardiac injury in COVID-19: A pathologic study. Circulation 2021;143:1031-42.
45. Boknäs N, Laine C, Hillarp A, Macwan AS, Gustafsson KM, Lindahl TL, *et al.* Associations between hemostatic markers and mortality in COVID-19 – Compounding effects of D-dimer, antithrombin and PAP complex. Thromb Res 2022;213:97-104.
46. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available from: https://www.covid19treatmentguidelines.nih.gov/. [Last accessed on 2023 Sep 25].
47. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, *et al.* Efficacy and safety of therapeutic-dose heparin versus standard prophylactic or intermediate-dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19: The HEP-COVID randomized clinical trial. JAMA Intern Med 2021;181:1612-20.
48. Stone GW, Farkouh ME, Lala A, Tinuoye E, Dressler O, Moreno PR, *et al.* Randomized trial of anticoagulation strategies for noncritically Ill patients hospitalized with COVID-19. J Am Coll Cardiol 2023;81:1747-62.
49. Qudus MS, Tian M, Sirajuddin S, Liu S, Afaq U, Wali M, *et al.* The roles of critical pro-inflammatory cytokines in the drive of cytokine storm during SARS-CoV-2 infection. J Med Virol 2023;95:e28751.
50. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020;5:811-8.

51. Ruiz-Ortega M, Ruperez M, Lorenzo O, Esteban V, Blanco J, Mezzano S, *et al.* Angiotensin II regulates the synthesis of proinflammatory cytokines and chemokines in the kidney. Kidney Int Suppl 2002;82:S12-22.
52. Hartmann C, Miggiolaro AF, Motta JD, Baena Carstens L, Busatta Vaz De Paula C, Fagundes Grobe S, *et al.* The pathogenesis of COVID-19 myocardial injury: An immunohistochemical study of postmortem biopsies. Front Immunol 2021;12:748417.
53. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, *et al.* Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. Cell Host Microbe 2016;19:181-93.
54. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, *et al.* An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med 2020;26:1636-43.
55. Sandoval Y, Januzzi JL Jr., Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19: JACC review topic of the week. J Am Coll Cardiol 2020;76:1244-58.
56. Libby P. The heart in COVID-19: Primary target or secondary bystander? JACC Basic Transl Sci 2020;5:537-42.
57. Morimoto S, Kato S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, *et al.* Role of myocardial interstitial edema in conduction disturbances in acute myocarditis. Heart Vessels 2006;21:356-60.
58. Capecchi PL, Laghi-Pasini F, El-Sherif N, Qu Y, Boutjdir M, Lazzerini PE. Autoimmune and inflammatory K(+) channelopathies in cardiac arrhythmias: Clinical evidence and molecular mechanisms. Heart Rhythm 2019;16:1273-80.
59. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019: Possible mechanisms. J Card Fail 2020;26:470-5.
60. Jammoul M, Naddour J, Madi A, Reslan MA, Hatoum F, Zeineddine J, *et al.* Investigating the possible mechanisms of autonomic dysfunction post-COVID-19. Auton Neurosci 2023;245:103071.
61. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, *et al.* Autonomic dysfunction in 'long COVID': Rationale, physiology and management strategies. Clin Med (Lond) 2021;21:e63-7.
62. Wang EY, Mao T, Klein J, Dai Y, Huck JD, Jaycox JR, *et al.* Diverse functional autoantibodies in patients with COVID-19. Nature 2021;595:283-8.
63. Wallukat G, Hohberger B, Wenzel K, Fürst J, Schulze-Rothe S, Wallukat A, *et al.* Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. J Transl Autoimmun 2021;4:100100.
64. Novak P, Mukerji SS, Alabsi HS, Systrom D, Marciano SP, Felsenstein D, *et al.* Multisystem involvement in post-acute sequelae of coronavirus disease 19. Ann Neurol 2022;91:367-79.
65. Trevino JA, Novak P. TS-HDS and FGFR3 antibodies in small fiber neuropathy and dysautonomia. Muscle Nerve 2021;64:70-6.
66. Mann R, Perisetti A, Gajendran M, Gandhi Z, Umapathy C, Goyal H. Clinical characteristics, diagnosis, and treatment of major coronavirus outbreaks. Front Med (Lausanne) 2020;7:581521.
67. Yu CM, Wong RS, Wu EB, Kong SL, Wong J, Yip GW, *et al.* Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J 2006;82:140-4.
68. Parise RS, Ramesh S, Govindarajulu M, Ajoolabady A, Moore T, Dhanasekaran M. COVID-19-induced cardiovascular damage differs from other prevalent viruses. Cardiol Plus 2021;6:231-45.
69. Li SS, Cheng CW, Fu CL, Chan YH, Lee MP, Chan JW, *et al.* Left ventricular performance in patients with severe acute respiratory syndrome: A 30-day echocardiographic follow-up study. Circulation 2003;108:1798-803.
70. Chong PY, Chui P, Ling AE, Franks TJ, Tai DY, Leo YS, *et al.* Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: Challenges in determining a SARS diagnosis. Arch Pathol Lab Med 2004;128:195-204.
71. Liu Y, Wu S, Qin M, Jiang W, Liu X. Prevalence of cardiovascular comorbidities in coronavirus disease 2019, severe acute respiratory syndrome, and middle east respiratory syndrome: Pooled analysis of published data. J Am Heart Assoc 2020;9:e016812.
72. Liu J, Xie W, Wang Y, Xiong Y, Chen S, Han J, *et al*. A comparative overview of COVID-19, MERS and SARS: Review article. Int J Surg 2020;81:1-8.
73. Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y. From SARS and MERS to COVID-19: A brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. Respir Res 2020;21:224.
74. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann Saudi Med 2016;36:78-80.
75. Ho JS, Tambyah PA, Ho AF, Chan MY, Sia CH. Effect of coronavirus infection on the human heart: A scoping review. Eur J Prev Cardiol 2020;27:1136-48.
76. Gupta MD, Kunal S, Girish MP, Goyal D, Malhotra RK, Mishra P, *et al.* Impact of COVID-19 vaccination on mortality after acute myocardial infarction. PLoS One 2023;18:e0291090.
77. Akhtar Z, Trent M, Moa A, Tan TC, Fröbert O, MacIntyre CR. The impact of COVID-19 and COVID vaccination on cardiovascular outcomes. Eur Heart J Suppl 2023;25:A42-9.
78. Jiang J, Chan L, Kauffman J, Narula J, Charney AW, Oh W, *et al.* Impact of Vaccination on major adverse cardiovascular events in patients with COVID-19 infection. J Am Coll Cardiol 2023;81:928-30.
79. World Health Organization. SAGE Updates COVID-19 Vaccination Guidance. Available from: https://www.who.int/news/item/28-03-2023-sage-updates-covid-19-vaccination-guidance. [Last accessed on 2023 Oct 02].
80. Driggin E, Maddox TM, Ferdinand KC, Kirkpatrick JN, Ky B, Morris AA, *et al.* ACC health policy statement on cardiovascular disease considerations for COVID-19 vaccine prioritization: A report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol 2021;77:1938-48.