Review Article

COVID-19-Induced Cardiovascular Damage Differs from other Prevalent Viruses

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Abstract

Viral infections persist globally, among all ages, gender, and ethnicity. Of particular importance is COVID-19, associated with asymptomatic to severe symptoms, including complications/mortality. Cardiovascular disease (CVD) involves heart and blood vessel disorders including coronary heart disease, cerebrovascular disease, peripheral artery disease, thrombosis, and more. CVD associated with severe COVID-19 includes heart failure, coronary artery disease, cardiomyopathy, hypertension, and cerebrovascular disease/stroke. Data were acquired from PubMed, Google Scholar, Centers for Disease Prevention and Control, and Lexi-Comp using the search terms "COVID-19 and cardiovascular pathology;" "COVID-19 induced CVD;" "Viral infection induced CVD;" and "Viral infection induced heart damage." COVID-19-induced CVD mechanisms include direct viral entry, inflammation, cytokine storm, hypoxia, interferon-mediated immune response, plaque destabilization, stress, and drug-induced causes. Other viral pathologies causing CVD include atherosclerosis, inflammation, cytokine storm, and plaque destabilization. Individual parameters, such as old age, males, and higher body mass index (BMI), are more likely to experience viral-associated complications, possibly explained by patient risk factors or comorbidities. Populations at higher risk include older males with an elevated BMI. Viral mechanisms associated with CVD are similar but differ in disease severity, potentially explained by diverse cytokine profiles where COVID-19 activates different types at higher quantities.

Keywords: *Cardiovascular disease; Cardiovascular pathology; COVID-19; Heart damage; Severe acute respiratory syndrome-coronavirus-1*

Introduction

The goals of this study were to compare severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) (COVID-19)-induced cardiovascular disease (CVD) with other common viruses and determine specific mechanisms of COVID-19-related CVD. Many viruses are associated with developing or worsening CVD. Patients at high risk for CVD or previously diagnosed have a higher prevalence of morbidity/mortality. The Centers for Disease Prevention and Control (CDC) reports heart disease is the leading cause of death, causing one in four deaths.[1] About three-fourth of CVD mortality occurs in low/middle-income underdeveloped countries.[2] Minimal studies are currently available, as of December 2021, relating economic income to COVID-19-induced CVD. Nghiem and Wilson (2021) suggested the possibility of unemployment rates during the COVID-19 pandemic in a high-income country causing significant health loss, increased CVD, and additional health system costs.[3] Singu *et al*. suggested an inverse correlation between low-income areas, food desert neighborhoods, and COVID-19 health complications.[4] Low-income areas with minimal access to healthy food options are

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at increased risk for CVD, which additionally can increase the risk for COVID-19 infection. Data are unclear to define a direct impact of economic income to COVID-19-induced CVD. The CDC reported 9% of 74,439 COVID-19 cases were associated with heart disease on March 28, 2020.[5] Others reported a five-fold increased risk of death in CVD (10.5%) versus non-CVD (2.3%).[6] Our study focused on COVID-19 and CVD globally. In comparison to COVID-19's pathologies leading to CVD, the mechanisms of other viruses were identified. The viruses, in this study, include COVID-19, influenza, H1N1, hepatitis, human immunodeficiency virus (HIV), and SARS.

Background

Multiple pathologies have been examined in association with the development of CVD. The common pathologies leading to CVD are aging, obesity, genetics, inflammation, infection, lifestyle, and diabetes mellitus. Most of these mechanisms can be controlled through lifestyle modifications and medicine. Preventative therapy is beneficial in nonmodifiable mechanisms.

Aging

Aging is a common nonmodifiable mechanism for developing CVD. Aging can naturally lead to the diagnosis of hypertension, a common risk factor for CVD.[7] Over the course of a lifetime, arteriosclerosis occurs, meaning the hardening of the arteries. This is the most common mechanism for developing age-induced CVD because the hardened arteries lead to increased arterial pressure and blood volume resistance. Hardened arteries initially develop from plaque buildup inside arterial walls causing a narrowed pathway for blood flow. Smaller vessels create pressure, limiting the ability of oxygen-rich blood to reach vital organ systems. These effects can lead to hypertension. Those of advanced age become more sensitive to salt, which can cause rising blood pressure or edema in ankles and feet. These effects are due to more sodium and water retention occurring with dietary salt intake. Heart disease develops when plaque builds up in coronary arteries, causing reduced blood flow to heart muscles, weakening them. Progressive changes in heart, artery structure, and function include diffuse intimal and medial thickening, increased stiffness, and reduced distensibility of central arteries.[8] Another risk factor is the number of stressful events the person has experienced throughout their lifetime. Stress increases blood pressure because endothelial and vascular smooth muscle cells shift phenotypes producing inflammatory cytokines. Stress leads to enhanced adrenergic signaling and increased renin-angiotensin-aldosterone system (RAAS) activation. RAAS causes more sympathetic outflow because of oxidative stress in the brain.[9] Production of angiotensin II, a potent vasoconstrictor, triggers the secretion of aldosterone (vasoconstrictor) and vasopressin (antidiuretic). When excess aldosterone is released, the hormone causes potassium loss and sodium retention, elevating blood volume and blood pressure. Vasopressin promotes free water reabsorption in the kidneys contributing to increased blood volume and pressure. With these effects in mind, age also increases a person's risk for contracting COVID-19. The CDC reports older adults to have a greater likelihood of severe COVID-19 with an increased risk of hospitalization requiring ventilator support or death. This risk is significantly increased for adults >50 years. Those >85 years have the highest chance of severe illness. Older adults with a preexisting CVD are also at increased risk for severe illness.

Obesity

Obesity is a common mechanism for developing CVD and can be prevented or controlled through lifestyle habits or pharmacotherapy. The CDC reports overweight (body mass index [BMI] >25, <30 kg/m^2), obesity (BMI >30, <40 kg/m^2) or severe obesity (BMI >40 kg/m^2) increases the risk for severe COVID-19 illness. The risk increases with increasing BMI. A study conducted across three China hospitals reported obese patients (defined as BMI >25 kg/m^2) having a longer hospital stay than nonobese with COVID-19, 23 versus 18 days.[10] The study showed obese patients had a higher prevalence of severe COVID-19 versus nonobese patients, 33.3% versus 14.7%. Obesity was associated with a three-fold increased risk for severe COVID-19, and each one-unit increase in BMI represented a 12% increased risk for severe COVID-19 infection. These results remained significant after adjusting for age, sex, smoking, hypertension, diabetes, and dyslipidemia. Obesity is a risk factor for causing CVD such as heart attack, stroke, and vascular dementia.[11] This is because of a greater amount of fatty materials or plaque in the arteries. As the coronary arteries become clogged or damaged, a heart attack could occur due to the blockage of blood flow to the heart. If blood flow is blocked from reaching the brain, a stroke or vascular dementia could develop. The CDC reports that obesity is linked to higher low-density lipoprotein (LDL), known as bad cholesterol, higher triglyceride (TG), and lower high-density lipoprotein (HDL), known as good cholesterol.[1] Visceral fat in obese patients affects hormones raising blood cholesterol, blood pressure, and an increased risk for type 2 diabetes mellitus.

The pathology for obesity and COVID-19 severity is not well understood. It is likely because of underlying low-grade chronic inflammation and suppressed innate

and adaptive immune responses in obese persons. Gao *et al*. stated the altered microenvironment could cause diverse viral mutations resulting in potential pathogenic variants responsible for causing more damage.[10] The mechanical dysfunction associated with obesity may increase the risk for severe lower respiratory tract infections or secondary infections.

Genetics

Several genes are associated with the etiopathology of CVD. Genetic factors play a role in high blood pressure, heart disease, diabetes, and other conditions. However, those sharing a family history of CVD may have similar environmental factors that may increase risk. Common inherited cardiac disorders include arrhythmias, congenital heart disease, cardiomyopathy, and high blood cholesterol.[12] A genetic mutation alters the way a protein functions, causing the body to process cholesterol differently, increasing the risk of blocked arteries leading to heart disease. A gene mutation can also affect the heart's structure and electrical system leading to abnormal heart rhythms and cardiovascular dysfunction.[13] The risk for heart disease is significantly elevated when defective genes are combined with aging, lifestyle, and obesity. About ½ of all Americans (43%) have at least one of three risk factors for heart disease including hypertension, high cholesterol, and smoking.[1] Those with CVD or inherited risk factors such as hypertension, diabetes, and obesity are at increased risk for worse clinical outcomes in COVID-19 infection.[14] It is likely genetics play a role in COVID-19-induced CVD, but data are unclear.

Inflammation

Inflammation can irritate blood vessels, promote plaque growth, loosen plaque in arteries, and trigger blood clots. The CANTOS clinical trial researched an injectable antibody type of anti-inflammatory medication in patients with a history of heart attacks with elevated inflammatory markers despite statin treatment.[15] Those treated with this anti-inflammatory reduced the chances of a heart attack or stroke by 15%. It also decreased angioplasty and bypass surgery by 30%. The inflammatory mechanism has not fully been proven to cause CVD, but inflammation is common in heart disease and stroke.[16] Smoking, hypertension, and elevated LDL can also lead to inflammation.

Lifestyle

Smoking and alcohol consumption are major, modifiable lifestyle factors leading to CVD. The World Health Organization reported smokers having a greater risk for severe COVID-19 disease than nonsmokers.[17] A large study across China reported 926 cases of nonsevere COVID-19 and 173 cases of severe symptoms. Among those with severe symptoms, 16.9% were current smokers and 5.2% were former smokers.[18] In the nonsevere group, 11.8% were current smokers and 1.3% were former smokers. This is likely because cigarette smoking affects the respiratory system by increasing the expression of angiotensin-converting enzyme 2 (ACE2) receptors. COVID-19 binds to these receptors for entry into the human body. Alcohol use disorder increases the risk for acute lung injury and severe COVID-19 infection. This is because alcohol causes lung injury in the upper respiratory airways. Nitric oxide, produced during alcohol metabolism, can deteriorate endothelial function or desensitize cilia affecting pathogen clearance. Chronic alcohol use alters glutathione homeostasis, resulting in more significant oxidative stress in the pulmonary environment. Alcohol also disrupts innate and adaptive immune responses by altering alveolar macrophages to phagocytose and clear bacteria, increasing the risk for severe infection.

Diabetes mellitus

Diabetes mellitus is a common mechanism for the development of CVD. The diagnosis of diabetes mellitus can be hereditary or environmental. Visceral fat around the abdomen can cause less response of the body to use insulin. When insulin is not used appropriately, blood sugar levels increase, causing damage to arteries increasing the risk for heart disease or circulatory diseases.[11] The CDC reported diabetic mellitus patients are twice as likely to develop CVD compared to nondiabetic mellitus patients.[19] This risk increases with long-standing diabetes mellitus, and also it is more likely to present with comorbid conditions, such as high blood pressure, elevated LDL, and elevated TGs.

Infection

Viral or bacterial infections can cause cardiomyopathy when the heart muscle is enlarged and cannot adequately pump enough blood to vital organs.[19] Chow *et al*. studied over 80,000 US adults hospitalized for flu from 2010 to 2018, where sudden, serious heart complications occurred in one out of every eight patients or ~12%.[20] Studies have shown HIV+ men had a 59% prevalence of coronary atherosclerosis versus 34.4% of HIV-men.[21,22] Another study has reported hepatitis C virus (HCV) patients are 28% more likely to develop CVD.[23]

Materials and Methods

Search strategy

This study was conducted by manually searching published articles up to December 2021 from the following databases: PubMed and Google Scholar. Search terms include the following: "COVID-19 and cardiovascular pathology;" "COVID-19 induced heart

disease;" "Viral infection induced heart disease;" "Viral infection induced cardiovascular damage;" "Influenza induced cardiovascular disease;" "Influenza induced heart damage;" "Common-flu induced cardiovascular disease;" "Common-flu induced heart damage;" "H1N1 induced cardiovascular disease;" "H1N1 induced heart damage;" "Hepatitis induced heart damage;" "Hepatitis induced cardiovascular disease;" "HIV induced heart damage;" "HIV induced cardiovascular disease;" "SARS-CoV-1 induced cardiovascular disease;" "SARS-CoV-1 induced heart damage;" "SARS induced heart damage;" and "SARS induced cardiovascular disease." We searched for relevant clinical content using CDC and Lexi-Comp. We manually searched references of selected articles for additional information. Articles were searched under English language restrictions.

Study selection

A total of 8105 articles were selected for our study. One thousand three hundred and forty-eight articles were associated with COVID-19 and cardiovascular pathology, and 6757 articles were linked to viral infection (influenza, common-flu, H1N1, hepatitis, HIV, and SARS-CoV-1) and cardiovascular pathology.

Inclusion criteria

Clinical trials, journal articles, meta-analyses, randomized controlled trials, reviews, and systematic reviews were included in this study if they represented information regarding COVID-19-induced cardiovascular damage or other prevalent viral infection-associated heart damage. We included these to gain better insight and knowledge on how COVID-19 causes CVD. We also wanted to compare COVID-19-induced cardiovascular pathology to how other prevalent viruses cause CVD.

Exclusion criteria

Pediatrics, heart transplants, drug-induced cardiovascular damage, and animal studies were excluded in this study because these subjects do not represent the general adult population. We formulated this criterion to focus on COVID-19's impact on the average adult cardiovascular system. Transplants do not reflect the majority or average population and could cause disruptions in our data, considering transplant patients may be more prone to infection-induced complications. Pediatrics and animal studies were excluded because they do not represent the average, functioning human adult cardiovascular system.

Results and Discussion

Proposed mechanisms of COVID-19-induced cardiovascular disease

Various pathologies have been proposed describing how COVID-19 causes CVD or damage. There is limited information related to the mechanism behind COVID-19-evoked myocardial injuries. The main pathologies are direct damages to systemic inflammation, cardiomyocytes, myocardial interstitial fibrosis, exaggerated cytokine response by Type 1 helper T cells, coronary plaque destabilization, hypoxia, and interferon (IFN)-mediated immune responses. Table 1 summarizes potential pathologies described across multiple studies including (1) direct cardiovascular entry, (2) inflammation, (3) cytokine storm, (4) hypoxia, (5) IFN-mediated immune response, (6) plaque destabilization, (7) stress, and (8) drug-induced. The myocardial injuries associated with COVID-19 are obvious by increased high-sensitivity cardiac troponin 1 (cTn1) levels. cTn1 is increased in patients suffering from severe COVID-19 disease versus those with moderate disease.[24-36] Tajbakhsh *et al*. reported 11.8% of deceased COVID-19 patients with no preexisting CVD experienced heart damage accompanied by a greater level of cTn1 or cardiac arrest during hospitalization.[24]

COVID-19 and direct cardiovascular entry causing cardiovascular disease

One hypothesis for developing COVID-19-induced CVD through direct heart injury is binding to ACE, ACE2, located in cardiomyocytes, pericytes, fibroblasts, endothelial cells, and leukocytes[37] which helps block the effects of angiotensin 2 on the lung and heart.[29] ACE2 receptors are also present across multiple organ systems where it is hypothesized to cause direct myocardial involvement leading to myocarditis in severe patient cases.[30,38] When the virus binds to the ACE2 receptor, inflammatory processes contribute to uncontrollable cytokine storm impacting the circulatory system, multiorgan failure, and subsequently death. Saba *et al*. reported spike protein (S1) of COVID-19 binds to ACE2, resulting in endocytosis and translocation of the virus and the enzyme into endosomes.[26] As COVID-19 binds to ACE2, there is an increased production of angiotensin 2 in the heart, liver, kidneys, and gastrointestinal tract, causing possible plaque rupture through activation of systemic inflammation.[26] Studies have shown that transmembrane serine protease 2 (TMPRSS2) aids in the entry of COVID-19, where the cell must express both ACE2 and TMPRSS2 for COVID-19 entry.[24,28,29] Magadum and Kishore (2020) referenced studies showing the inhibition of TMPRSS2 blocked viral entry, reducing viral infection and severity of lung pathology with increased survivability in mouse models, indicating a potential therapeutic target to decrease infections and complications.[6,39,40] TMPRSS2 and ACE2 are both expressed in the lungs, heart, gut smooth muscle, liver, kidney, neurons, and immune cells.[28,41] Comparatively, this entryway is the same

Table 1: Coronavirus disease 2019 and possible mechanism of cardiovascular damage

COVID-19		
Cardiovascular conditions	**Cardiovascular pathology**	**Author**
Acute myocardial injury	Direct viral entry through ACE2 receptor	Magadum and Kishore[6]
Myocarditis		Tajbakhsh *et al*.[24]
Coronary heart disease		Cao Q *et al*.[25]
Arrhythmia		Saba *et al*.[26]
Hypertension		Hammoud *et al*.[27]
Cardiac arrest		Liu *et al*.[28]
Stress-induced cardiomyopathy		Kurz and Eberli[29]
Cardiogenic shock		Mokhtari *et al*.[30]
Ischemic stroke		Bojkova *et al*.[31]
Cardiac injury	Systemic inflammation	Magadum and Kishore[6]
Inflammatory Cardiomyopathy		Cao Q *et al*.[25]
Venous thromboembolism		Saba *et al*.[26]
		Kurz and Eberli[29]
		Mokhtari *et al*.[30]
		Amraei and Rahimi[32]
		Tschöpe *et al*.[33]
	Cytokine storm	Magadum and Kishore[6]
		Saba *et al*.[26]
		Kurz and Eberli[29]
		Mokhtari *et al*.[30]
		Amraei and Rahimi[32]
		Yuan *et al*.[34]
	Hypoxia	Magadum and Kishore[6]
		Cao Q *et al*.[25]
		Kurz and Eberli[29]
	Interferon-mediated immune response	Magadum and Kishore[6]
		Maxwell *et al*.[35]
	Plaque destabilization	Magadum and Kishore[6]
		Saba *et al*.[26]
		Mokhtari *et al*.[30]
		Allegra *et al*.[36]
	Stress	Cao Q *et al*.[25]
	Drug-induced	Magadum and Kishore[6]
		Cao Q *et al*.[25]

COVID-19: Coronavirus disease 2019, ACE2: Angiotensin converting enzyme2

mechanism as SARS-CoV-1 (SARS). Both SARS-CoV-1 and SARS-CoV-2 entry, into the host, require binding of the spike protein to ACE2 and spike protein priming mediated by TMPRSS2, cathepsin B, and cathepsin L.[33]

Bojkova *et al*. presented evidence indicating COVID-19 was linked to cytotoxic effects by blocking the beating function of cardiomyocytes and cardio spheres, suggesting a possible detrimental effect on the human heart.[31] Cardiomyocytes were less susceptible to COVID-19 infection and cytotoxic effects than TMPRSS (2+) CaCo (2-) cells, representing a faster and more severe cytotoxic response. These conditions may be related to high virus concentration and long exposure time. Patients with a past medical history of CVD have a higher risk for severe illness in COVID-19 disease. This could be due to ACE2 receptors that are present on the cardiac muscles.[42] Patients with CVD have a higher chance of developing acute coronary syndrome (ACS) in acute COVID-19 infections. This disease-enhanced myocardial demand could lead to myocardial injury or infarction.

ACE2 inhibitors and angiotensin receptor blockers (ACEi and ARBs) are common blood pressure medicines taken by those with hypertension. Patients taking these drugs

have an increased number of ACE2 receptor expressions. COVID-19 causes damage to cardiomyocytes by targeting ACE2 receptors and triggering inflammatory responses. Direct injury to the myocardial cells may lead to cytokine storm and/or an imbalance of oxygen supply caused by acute respiratory distress syndrome (ARDS). As COVID-19 binds to ACE2 receptors, these are downregulated, and the expression of angiotensin 2 is increased, causing vasoconstriction, increased blood pressure, increased aldosterone secretion, and sodium/water retention, sympathetic activity, cardiovascular fibrosis, and hypertrophy. This subsequently may contribute to more stress and dysregulation in the vascular because of RAAS imbalance and the risk for multiorgan damage.[6,27] The ACE1, angiotensin 2, and angiotensin 1 receptor promote the development of atherosclerotic lesions, aneurysms, and proinflammatory cytokine secretion which clarifies why RAAS imbalance and COVID-19 entry through ACE2, causing downregulation of this receptor, would be associated with CVD.[27,43] Circulating ACE2 receptor levels in patients are 50% higher in men than women in heart failure,[28,44,45] which may explain the higher prevalence in the male population as described in Table 2.[46,47]

The severity of symptoms related to COVID-19 and CVD might be associated with the high expression of ACE2 in cardiac cells.[48]

COVID-19 and systemic inflammation causing cardiovascular disease

After COVID-19 initially enters the body through respiration, the virus binds to the ACE2 receptors on cardiac cells, where it will begin inflammatory processes disrupting the circulatory system. After ACE2 binding and cell entry, the body's immune response activates inflammatory mechanisms to rid the virus from circulation. Inflammation and cytokine storm can lead to vascular inflammation, plaque instability, or myocardial inflammation.[6] Studies have reported after acute COVID-19 infection, myocardial damage occurs in patients with increased inflammatory activity, platelet activation, increased thromboxane synthesis, and impaired fibrinolytic function.[24,26] Increased inflammation associated with cytokine storm can lead to vascular and myocardial inflammation or plaque destabilization leading to a heart attack, cardiomyopathy, and/or heart failure.[6,49,50] Type 1 IFN responses are impacted by COVID-19 infection where minimal amounts of IFN-α or β have been detected in the blood. This suggests a blunted type 1 IFN where the dysregulated response allows successful infection, replication, and excessive inflammation.[35,51,52]

Increases in biomarkers (troponin, N-terminal pro-brain natriuretic peptide, and D-dimer) are common, especially in severe systemic inflammation and ARDS associated with poor outcomes.[29] Systemic inflammation involves endothelial cell dysfunction and atherosclerosis and increases the risk of cardiac ischemia. In COVID-19-induced cardiac injury, destruction of infected cells leads to systemic release of interleukin-1β (IL-1β) because of stimulation of NLRP3 inflammasome, a part of the innate immune response to viral infections.[30] The NLRP3 inflammasome is correlated with cytokine storm in severe COVID-19 disease.[48] Coronavirus structural and accessory proteins trigger inflammasome activation. Inhibition of NLRP3, by a selective MCC950 suppressor, resulted in decreased interleukin IL-1β secretion from spike protein-stimulated macrophages. Postmortem samples showed COVID-19 induces inflammasome activation in primary human monocytic cells and mimic the release of lactate dehydrogenase from infected monocytes. Recent reports showed COVID-19 directly infects human monocytic cells and promotes activation of NLRP3 and lytic cell death.[48,53,54] NLRP3 is involved with the development of multiple CVD such as myocardial infarction, atherosclerosis, and cardiac remodeling.[48] The response by NLRP3 inflammasome results in hyperinflammatory responses by intensifying inflammatory effects of COVID-19 or by altering the ACE2/angiotensin pathway, which is also associated with clinical effects of coronavirus infections.[48,55]

Table 2: Comparison of patient parameters increasing the risk for cardiovascular dysfunction or disease

Data source	Location	Viral infection	Age	Sex	BMI (kg/m^2)
CDC	United States	COVID-19	≥65	Male	≥30
CDC	United States	Common Flu	≥65*	-	≥40
CDC	United States	H1N1	≥65	-	≥40
Babiker *et al*.[46]	English Studies	Hepatitis (HCV)	Average 40s (31->65)	Male	-
CDC	United States	HIV	Older age	Male	≥25
Venketasubramanian and Hennerici[47]	Singapore	SARS	Average 63 (39-68)†	Females‡	-

*Those with past medical history or heart disease or stroke are at higher risk for serious flu complications, †Specifically for ischemic stroke, ‡Specifically for ischemic stroke. CDC: The Centers for Disease Prevention and Control, BMI: Body mass index, COVID-19: Coronavirus disease 2019, HCV: Hepatitis C viral, HIV: Human immunodeficiency virus, SARS: Severe acute respiratory syndrome

Studies have hypothesized that vascular issues associated with COVID-19 have a strong correlation to neutrophil extracellular traps (NETs).[35] In COVID-19, NETs have been associated with organ damage and mortality in severe cases. The upregulation of cytokines, including CCL20, IL-6, tumor necrosis factor-alpha (TNF-α), and IL-1β, are related to NET regulation and production. IL-6 and TNF-α are inducers of NETosis. Mast cells and NETs release IL-17.[35,56] Increased IL-17 has been found in thrombi of acute myocardial infections,[57] so IL-17 in NETs may play a role in promoting thrombus development in COVID-19 patients.[35]

COVID-19 and cytokine storm causing cardiovascular disease

Cytokine storm is a predominant mechanism leading to CVD. Cytokine storm is characterized explicitly by increased pro-inflammatory cytokines such as IL-1, IL-6, interferon-γ, and TNF-α. COVID-19-associated cytokine storm has been a predominant mechanism for causing organ damage and injury. The specific cytokines involved with this pathology include the following: IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, monocyte chemoattractant protein (MCP-1), MIP 1-α, hepatocyte growth factor, TNF-α, ferritin, C-reactive protein (CRP), and vascular endothelial growth factor.[6,26,32,34] These elevated markers could lead to conduction abnormalities, atrial fibrillation, and sustained cardiac injury. Decreased CD4+, CD8+, and total T-cell numbers have been associated with reduced survival rates.[26,38] High ferritin and IL-6 plasma values have been correlated with mortality in COVID-19 infection.[26,58] The increased number of inflammatory cytokines can lead to atherosclerosis, procoagulant activity, and hemodynamic instability, resulting in ischemia and thrombosis.

Reports have shown that myocardial injury occurs with COVID-19 infection due to cytokine storm, stimulated by an imbalanced response involving Th1 and Th2 cells. This can also cause respiratory dysfunction, hypoxemia, shock, or hypotension. These effects are because of insufficient oxygen supply to the myocardium in pulmonary infections. Myocardial damage occurs with infection because there is an increased burden on the heart and an imbalance of oxygen supply and demand. This is especially true for patients with chronic CVD. Cytokine storm could be involved with effects observed causing myocardial damage. Therefore, cytokine storm is closely responsible for disease severity and is associated with cardiac inflammation. Cytokine storm may also cause some cardiovascular symptoms such as tachycardia, hypotension, left ventricular dysfunction, and direct cardiotoxicity, leading to conduction dysfunction, atrial fibrillation, and injury.[6] Cytokine expressions, IL-1, IL-6, and TNF-α, might cause the development of arrhythmias in COVID-19 patients.[48,59]

COVID-19 and plaque destabilization causing cardiovascular disease

Plaque destabilization could result from the effects of inflammation activating the clotting cascade leading to an increased risk of venous thromboembolism. Disseminated intravascular coagulation (DIC) is the cause of multiorgan damage in situations outside of COVID-19 or other viral infections. A 2020 study reported DIC was found in 71.4% of non-survivors with COVID-19 versus 0.6% in survivors.[6,60] Infections are frequently the cause of DIC development because damages to the endothelial cells and monocytes induce significant cytokine production. Toxic cytokines cause dysregulation due to the production of von Willebrand factor, tissue factor, increased thrombin which stimulates platelets and activates fibrinolysis.[36] With RAAS imbalance and high levels of angiotensin 2, the pro-inflammatory and prothrombotic activity of angiotensin 2 may rupture a plaque leading to a thrombotic event.[26] Pro-inflammatory mediators, such as IL-1β, IL-6, IL-12, MCP-1, IFN-γ, and IFN-inducible protein, increased in COVID-19, are associated with coagulation activation, increasing the risk for developing a thrombus.[30]

COVID-19 and stress-causing cardiovascular disease

COVID-19 infection induces stress on the organ systems, activating various inflammatory mediators, cytokine storm, and hypoxia, leading to the development of multiorgan failure. During infection, multiple signaling pathways are activated, and the heart muscle can be overwhelmed because of the stressful working conditions of the immune system.

COVID-19 and drug-induced cardiovascular disease

Antiviral drug agents used to treat COVID-19 for multiorgan dysfunction may induce cardiac toxicity.[6] Lopinavir/ritonavir has been associated with causing hypertension which could put a patient at risk for cardiovascular complications during COVID-19 infection.[61] Hydroxychloroquine use has significant adverse reactions, including cardiomyopathy, a cardiovascular complication in COVID-19 patients. However, this option is not recommended for COVID-19 treatment due to the lack of benefit and potential for toxicity.[62] Dexamethasone, a common steroid used in severe COVID-19, has been associated with cardiac arrhythmias, cardiac failure, cardiomegaly, hypertension, myocardial rupture after a recent myocardial infarction,

thromboembolism, and vasculitis.[63] Baricitinib or tocilizumab is suggested in severe disease in patients with certain clinical implications, where baricitinib is associated with deep vein thrombosis, pulmonary embolisms, and venous thrombosis.[64] Tocilizumab has been linked to deep vein thrombosis, hypertension, and septic shock.[65]

Association of common flu and cardiovascular disease

Common flu or seasonal influenza has a history of causing cardiovascular complications in those with CVD risk factors. The pathologies associated with how influenza viral infection leads to cardiovascular dysfunction are summarized in Table 3.[66-68] The CDC reports people with heart disease or those with a past medical history of a stroke are at higher risk for developing serious flu complications.[1] Kwong *et al*. determined the risk of a heart attack was six times higher within 1 week of confirmatory influenza infection.[69] Chow *et al*. studied eight previous flu seasons from 2010 to 2011 through 2017–2018 where ~12%, or 1 out of 8, patients presented with sudden, serious heart complications.[20] Haidari *et al*. studied the vascular effects of influenza and the effects on atherosclerotic arteries in mice subjects.[67] For the first time, the study represented the influenza virus infection directly infecting the atherosclerotic arteries. The influenza infection was associated with systemic and arterial pro-inflammatory changes. This is significant evidence showing that influenza infection is directly correlated to worsening CVD in patients with a history of atherosclerosis. Influenza-infected patients with atherosclerotic plaque buildup in the coronary arteries would be at an increased risk for plaque dislodging, causing myocardial infarction or stroke. Flu infection places a patient's heart under intense stress, while the body fights off the infection. Stress occurs because the heart is working harder than normal. An increased heart rate, increased blood pressure, and increased intrinsic stress hormones reflect stress on the heart. A healthy human heart may be able to tolerate the excess workload, but an aged, diseased, or at-risk heart may not be able to handle the compensation, potentially leading to cardiovascular complications. Along with the stress load, influenza viral infection induces proinflammatory mediators, leading to plaque destabilization and the risk of having a heart attack or stroke. Other pathologies related to influenza infection-associated cardiovascular outcomes include cytokine storm, another mechanism similar to COVID-19. However, the reason for different health outcomes when an at-risk patient has influenza versus COVID-19 is likely because of fewer cytokines activated during infection. This is most likely one of the reasons for differing symptoms and severity between the two infections. Influenza H5N1 has specifically been associated with increases in IFN-β, IL-2, IL-4, IL-5, IL-6, IL-10, and IP-10.[34,66] Overall, the comparison of influenza and COVID-19 viral infection-associated CVD pathologies are similar in inducing poor health outcomes. The major difference between influenza and COVID-19 is cytokine activation related to cytokine storm. A major similarity between the two infections is the evidence shown in Table 2, representing the patient-specific identifiers for those at risk of developing serious complications from the infection. These factors should be considered during preventative therapy and acute/chronic treatment to avoid potentially serious consequences such as morbidity and/or mortality.

Table 3: Common flu infection and mechanism of cardiovascular dysfunction

Common flu		
Cardiovascular disease	**Cardiovascular pathology**	**Author**
Arrhythmia	Cytokine storm	Tschöpe *et al*.[33]
Inflammatory cardiomyopathy	Atherosclerosis	Yuan *et al*.[34]
Stroke	Inflammation	Olbei *et al*.[66]
Myocarditis	Plaque destabilization	Haidari *et al*.[67]
Acute myocardial infarction		Bhugra *et al*.[68]
Heart failure	Stress	

Association of H1N1 and cardiovascular disease

H1N1 or "swine flu" was a new influenza A strain detected in 2009, resulting in a pandemic. Those at "high risk" for severe complications from the flu were likely to be hospitalized during the pandemic. The high-risk group included those with heart disease, higher BMI, and more. These factors relate to COVID-19 patient groups at increased risk for hospitalization, serious complications, or mortality. These patient identifiers are summarized in Table 2. Similar to common flu, those infected with H1N1 presenting with CVD risk factors or a past diagnosis of CVD were more likely to have worsening chronic conditions. Karjalainen *et al*. (1980) reported 9% of patients infected with H1N1 were diagnosed with myocarditis.[70] Cardiologists reported those having a fatal myocardial infarction were related to risk factors for CVD, not the influenza infection.[71] The fatality was likely caused by the body's immune reaction and combined risk factors, causing a more severe consequence.

The common pathologies for H1N1-associated cardiovascular dysfunction include atherosclerosis involvement, cytokine storm, and inflammation. These are shown in Table 4. Golabchi and Sarrafzadegan reviewed H1N1 and its effects on the cardiovascular

system identifying atherogenesis as a major mechanism caused by H1N1 infection.[72] The reason for this suspected mechanism was the presence of a positive correlation between antibodies to influenza A virus and antibodies to oxidized LDL titers, indicating an activated autoimmune system may be susceptible to this pathway. It is common across all viruses and pathologies that cardiovascular dysfunction or disease is brought about because of the body's natural immune system response. Other mechanisms proposed causing cardiovascular system dysregulation are increased pro-inflammatory and prothrombotic cytokines, endothelial dysfunction, increased plasma viscosity, psychological stress, loss of anti-inflammatory properties of HDL, increase in an invasion of macrophages into arterial walls, reduction in clotting time, and apolipoprotein-E deficiency.[72] Many of these pathologies and their impact on the heart are similar to how COVID-19 causes cardiovascular dysfunction, such as increased demand, decreased perfusion or supply, stress, pro-inflammatory and prothrombotic cytokine expression, atherosclerotic changes, and possible plaque destabilization, leading to a heart attack or stroke. Yuan *et al*. referenced cytokine storm as a mechanism for the H1N1 pandemic.[34] A comparison with coronaviruses and other influenza viral infections revealed COVID-19 activated a larger number of cytokines versus H1N1 infection, which could explain the greater disease severity of COVID-19 in infected patients leading to morbidity and/or mortality. Systemic inflammation and thrombogenic responses causing atherosclerotic plaque destabilization is another mechanism for influenza-type infections to cause cardiovascular system effects leading to an increased risk for ACS.[73,74] This inflammatory reaction occurs in the coronary bed and atherosclerotic plaques leading to endothelial dysfunction, vasoconstriction, platelet activation, and dysregulation of the coagulation system.[68] Along with those effects, the brain increases sympathetic activity and metabolic demand. Changes in circulatory volume and vascular tone cause plaque destabilization, increasing the risk for acute myocardial infarction.[75]

Association of hepatitis and cardiovascular disease

Research suggests HCV infection is a risk factor for developing CVD, but the data are mixed and not directly proven yet. The pathologies for cardiovascular system dysfunction associated with hepatitis infection are summarized in Table 5. The pathologies are similar to the other viral infections included in this study: Atherosclerotic pathways, inflammation, and cytokine storm. A different mechanism specific to hepatitis versus the other viruses is the relationship with diabetes mellitus patients in inducing cardiovascular system effects. HCV infection acts on glucose and lipid metabolism resulting in insulin resistance, steatosis, and type 2 diabetes.[46,76] All play key roles in the development of atherosclerosis. Other pathways leading to increased atherosclerosis include endothelial dysfunction, direct vascular invasion, increased release of pro-inflammatory markers, and downregulation of anti-inflammatory mediators.[46] Inflammatory myocarditis associated with HCV is likely the cause of immune-mediated effects and viremia, similarly with the suspected COVID-19 pathology.[33] Increased release of pro-inflammatory markers such as IL-6, TNF-α, CRP, and fibrinogen have been associated with HCV and can lead to chronic inflammation increasing atherosclerosis. Anti-inflammatory mediators, such as adiponectin, are decreased in HCV, which also plays a role in chronic inflammation. A high TNF-α/adiponectin ratio has been identified in HCV patients related to the process of atherosclerosis development and a heightened risk for developing CVD.[77] The cytokine storm pathology of HCV is different from COVID-19 regarding the number of cytokines activated, which may contribute to acute worsening of disease leading to morbidity and mortality in COVID-19 patients. Hepatitis was associated with a lesser number of cytokines released when compared to COVID-19 infection in a quantification analysis.[34]

Table 4: H1N1 infection and mechanism of cardiovascular dysfunction

H1N1		
Cardiovascular disease	**Cardiovascular pathology**	**Author**
Myocarditis	Atherosclerosis	Yuan *et al*.[34]
Acute coronary syndrome	Cytokine storm	Bhugra *et al*.[68]
Acute heart failure	Inflammation	Golabchi and Sarrafzadegan[72]
Arrhythmia		Falsey *et al*.[73]
Myocardial infarction		Julkunen *et al*.[74]
Stroke		Corrales-Medina *et al*.[75]

Table 5: Hepatitis infection and mechanism of cardiovascular dysfunction

Hepatitis		
Cardiovascular disease	**Cardiovascular pathology**	**Author**
Myocarditis	Atherosclerosis	Tschöpe *et al*.[33]
Cardiomyopathy	Inflammation	Yuan *et al*.[34]
Heart failure	Cytokine storm	Babiker *et al*.[46]
Myocardial infarction	Diabetics	Adinolfi *et al*.[76]
Stroke		Durante-mangoni *et al*.[77]
Arrhythmia		

Association of human immunodeficiency virus and cardiovascular disease

People living with HIV are experiencing heart disease and related complications at faster rates than people without HIV.[78] The proposed mechanisms for HIV-associated CVD are listed in Table 6. The pathologies are similar when compared to COVID-19 and other viral infections. Similar pathologies include atherosclerosis development, inflammation, and cytokine storm. Differing pathologies include hypercoagulability leading to a thrombus, autoimmunity, and drug-induced effects with the treatment of antivirals. However, these pathologies are likely to play roles in the other viral infections but may be less pronounced. Atherosclerosis development is a common pathology leading to CVD among most viral infections. Evidence has shown, HIV infection directly inactivates inflammasome, mediating the release of inflammatory cytokines such as IL-1β and IL-18 which aid in atherosclerotic progression.[79] John Hopkins determined men with long-term HIV are at an increased risk for developing plaque in coronary arteries, regardless of other risk factors than men without HIV.[78] Noncalcified coronary artery plaques, shown on CT angiography, were more prevalent and extensive in HIV-infected men. Because noncalcified plaques are more likely to trigger the development of a clot, this finding suggests an increased risk of having a myocardial infarction. This characteristic plays a role in the thrombus pathology proposed for HIV-induced CVD. Additionally, John Hopkins studied abnormal stress responses of HIV patients who had not developed plaque where the response was similar to those with severe coronary artery disease and is a predictor for future cardiovascular events. This response might be explained due to people living with HIV having higher levels of inflammation and immune activation, even with undetectable HIV levels in the blood. This mechanism plays a role in the commonly proposed pathology of inflammation and autoimmunity, leading to CVD. Inflammatory myocarditis associated with HIV is likely from immune-mediated effects and viremia, similarly to the suspected COVID-19 pathology.[33] Opportunistic infections can also play a role in developing CVD because people living with HIV are immunocompromised; therefore, these patients are more at risk for developing infections resulting in different disease severity and complications.[80,81] Cytokine storm has been identified in people living with HIV infection and is a proposed mechanism for developing CVD in these patients. This is commonly seen in COVID-19 patients and is likely responsible for the increased severity of the infection. Hepatitis B was associated with less cytokine activation when compared with coronaviruses like COVID-19; however, hepatitis C activated a high number of cytokines resembling COVID-19.[34] Hepatitis C is a more severe infection than hepatitis B, which could be explained by cytokine storm activation. This can be compared to COVID-19 in how cytokine storm activation causes detrimental effects. Further research is needed to compare hepatitis C and COVID-19 regarding cytokine storm profiles directly. HIV drugs have been associated with inducing CVD in some patients. Protease inhibitors, nucleoside/nucleotide reverse transcriptase inhibitors, integrase inhibitors, and entry inhibitors negatively impact

Table 6: Human immunodeficiency virus infection and mechanism of cardiovascular dysfunction

HIV		
Cardiovascular disease	**Cardiovascular pathology**	**Author**
Myocarditis	Inflammation	Tschöpe *et al*.[33]
Cardiomyopathy	Atherosclerosis	Yuan *et al*.[34]
Heart failure	Thrombus	Kearns *et al*.[79]
Arrhythmias	Drug-Induced	Johns Hopkins[15]
Diastolic dysfunction	Cytokine storm	Thienemann *et al*.[80]
Asymptomatic left ventricular dysfunction	Direct infection	Saad and Ntusi[81]
Myocardial fibrosis	Autoimmunity	
Myocardial steatosis	Opportunistic infections	
Pulmonary hypertension		
Peripheral arterial disease		
Stroke		
Infective endocarditis		
Coronary artery disease		

HIV: Human immunodeficiency virus

cholesterol levels and can cause insulin resistance involved in the development of CVD.[80]

Association of severe acute respiratory syndrome and cardiovascular disease

SARS-CoV-1 is a coronavirus like COVID-19 (SARS-CoV-2). Similar pathologies resulting in CVD between the two coronaviruses include direct entry through ACE2 receptor, inflammation, and activation of a cytokine storm. These are listed in Table 7. Both coronaviruses enter the cardiovascular system by binding the ACE2 receptors present on cardiomyocytes, pericytes, fibroblasts, endothelial cells, and leucocytes, as described in the COVID-19 section. Subsequently, the immune system activates inflammatory mediators to rid the viral material causing damage to the heart. Inflammatory myocarditis caused by coronaviruses has the same suspected pathology consisting of immune-mediated effects.[33] SARS-CoV-1 directly induces myocardial inflammation and downregulates myocardial ACE2, contributing to heart function abnormalities and cardiac consequences.[30] The major difference between SARS-CoV-1 and SARS-CoV-2 are the effects caused by cytokine storm. Both infections are associated with the activation of cytokine storm; however, different cytokines and a smaller number of cytokines are activated with SARS-CoV-1 infection versus SARS-CoV-2 infection. Activated cytokines related to SARS-CoV-1 are the following: IL-1β, IL-5, IL-12, IFN-γ, IP-10, and MCP-1.[34] The lesser degree of activated cytokines could explain why SARS-CoV-1 was a less severe outbreak than SARS-CoV-2.

Finally, Table 2 displays individual patient parameters that may place a person at risk for infection and complications arising because of infection. Across most infections, older age, males, and a higher BMI are associated with an elevated risk. This could be explained by considering the aging and obesity pathologies relating to the development of CVD. With older age, there is a greater incidence of hypertension, vascular damage, and reduced immune system function that can increase a person's risk for COVID-19 infection and cardiovascular complications. Obesity also alters immune system function, and the increased fatty tissue causes more stress on the heart and arteries. COVID-19 specifically binds to ACE2 receptors for viral entry, which are increased in the male population versus females. Smoking is also known to increase ACE2 receptor expression, as well as, contribute to CVD. It is crucial to note that traditional risk factors for CVD development such as high cholesterol, hypertension, diabetes, family history of CVD, and smoking play significant roles in the development of viral-induced CVD. It is important to identify these risks in patients early on to reduce the chance of a virus progressing into a heart attack or other cardiovascular complication. Medication adherence for those with a preexisting CVD and lifestyle modifications, like smoking cessation, healthy eating habits, and increased physical activity are important for CVD risk reduction and prevention.

Table 7: Severe acute respiratory syndrome-coronavirus-1 infection and mechanism of cardiovascular dysfunction

SARS		
Cardiovascular disease	**Cardiovascular pathology**	**Author**
Acute cardiac injury	ACE2 receptor entry	Liu *et al*.[81]
Ischemic stroke	Inflammation	Mokhtari *et al*.[30]
Arrhythmias	Cytokine storm	Tschöpe *et al*.[33]
Inflammatory Cardiomyopathy		Yuan *et al*.[34]
Systolic and diastolic abnormalities		

SARA: Severe acute respiratory syndrome, ACE2: Angiotensin-converting enzyme2

Differences between COVID-19 and other viral infections causing cardiovascular disease

Various cardiovascular complications have been associated with COVID-19, common flu, H1N1, hepatitis, HIV, and SARS. These cardiovascular conditions are listed in Tables 1,3-7. The differing pathologies between the two coronaviruses, COVID-19 and SARS, from the other viral infections are the ability of the coronavirus to bind to ACE2 receptors for entry into the human host. ACE2 receptor entry allows direct access into the circulatory system and cardiovascular system, which can transmit the virus to other major organ systems and cause major health complications. Each viral infection in this study has some association with activating cytokine storm leading to severe symptoms and CVD. COVID-19 is associated with the activation of a greater number of various cytokines, which likely contribute to the more severe symptoms and health complications seen during the COVID-19 pandemic. The cytokine profile associated with COVID-19 infection includes IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP 1-α, hepatocyte growth factor, TNF-α, ferritin, CRP, and vascular endothelial growth factor.[6,26,32,34] The cytokines associated with influenza infection include IFN-β, IL-2, IL-4, IL-5, IL-6, IL-10, and IP-10.[34,66] Yuan *et al*. reported critical H1N1 infection was associated with a greater number of activated cytokines as compared to severe H1N1 and mild H1N1, with mild infection activating the least amount of cytokines.[34] The individual cytokines could not be identified from the

study. The cytokines associated with hepatitis infection include IL-6, TNF-α, CRP, and fibrinogen. Yuan *et al*., reported additional cytokine activation, but the individual cytokines could not be identified from the study.[34] The cytokines associated with HIV infection include IL-1β and IL-18.[79] The cytokines associated with SARS infection include IL-1β, IL-5, IL-12, IFN-γ, IP-10, and MCP-1.[34] The larger amount of cytokines activated during cytokine storm, displayed by COVID-19, reflects the severity of symptoms and the risk for organ dysfunction or cardiovascular complications and increased morbidity/mortality rates. Cytokine storm has been a popular pathology to study COVID-19 secondary disorders because of the cytokine profile difference compared to other common viral infections.

Conclusion

Overall, it is clear each viral infection discussed in this study (COVID-19, common flu, H1N1, hepatitis, HIV, and SARS) is related to poor CVD outcomes in some patients. Most of the cardiovascular complications occurring during infection likely result from the body's immune system response to the infection itself, rather than the virus causing direct toxicity. There is significant evidence of COVID-19, causing cardiovascular damage through direct effects, but it is more likely infection-induced CVD results from secondary injury. Respiratory infections or viral infections presenting with respiratory signs and symptoms should be acknowledged and closely monitored. Mechanistically, lung infections can trigger heart infections as the virus travels through the blood into the cardiovascular system. If the virus resides in the heart, signs, and symptoms of cardiovascular involvement will present as the heart works harder to rid the virus and risk the possibility of causing internal heart damage. Vaccinations are standard preventable methods used for most viruses and should be recommended for CVD patients or those at risk for having CVD or event in the future. People most at risk for viral-induced complications are older age, obese, diagnosed with diabetes mellitus, or have a family history of CVD. Preventative therapy, lifestyle modifications, and healthcare provider awareness are key in avoiding these complications and pathologies involving viral-associated cardiovascular dysfunction.

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Conflicts of interest

There are no conflicts of interest.

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