Cardiovascular Complications in Patients with COVID-19: a comprehensive overview

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Abstract:

Although COVID-19 initially affects the respiratory system, several studies have drawn significant attention to the growing hypothesis that the infection is associated with direct and indirect cardiovascular complications that may negatively influence the outcome of diseased patients. We review the current literature to investigate the complications caused by COVID-19 in the heart and the vascular system. We also analyse the proposed mechanisms of cardiovascular involvement. The cardiovascular complications include myocarditis, myocardial injury, heart failure, arrhythmias as well as venous and arterial thrombosis, which are associated with elevated morbidity risk and adverse outcomes. The pathophysiological mechanisms that explain the cardiovascular complications include inflammation, endothelial dysfunction, an excessive storm cytokine release, coagulation disturbances, and cell hypoxia. Patients with underlying cardiovascular disease (CVD) tend to have worse outcomes compared to those without CVD. Arterial thrombosis seems to be associated with coagulopathy and increased D-dimer concentrations and can manifest in patients with no pre-existing comorbidities, atherosclerosis, or blood-clotting disorders. The rate of successful revascularization is lower than expected and is associated with a virus-related hypercoagulable state. Due to these adverse events critical diseased patients often require care from a multidisciplinary care team.

Keywords: SARS-CoV2; COVID-19; cardiovascular; stroke; limb ischemia; coagulopathy

INTRODUCTION

Severe acute respiratory syndrome caused by coronavirus 2 (SARS-CoV2; also known COVID-19) has been associated with high morbidity and mortality. According to the World Health Organization (WHO), as of the 1st of June 2021, there had been 170.426.245 confirmed cases of COVID-19, including 3.548.628 of deaths globally.[1]

The most common symptoms of COVID-19 are fever, dry cough, and tiredness. Less common symptoms that may affect some patients include loss of taste or smell, persistent pain or pressure in the chest, headache, sore throat, nasal congestion, aches and pains, diarrhoea, and a skin rash.[2] COVID-19 can cause upper respiratory system infection or pneumonia, which may lead to severe respiratory failure.[2] However, several recent studies have drawn significant attention to the growing hypothesis that SARS-CoV-2 is associated with direct and indirect cardiovascular complications, including acute myocardial injury and myocarditis, arrhythmias, heart failure, arterial and venous thromboembolism (VTE) and cerebrovascular events.[3-6]

We review the current literature to investigate the complications caused by SARS-CoV-2 in the heart and the vascular system. We also analyse the proposed mechanisms of cardiovascular involvement.

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COVID-19 MECHANISM OF HUMAN CELL INVASION

COVID-19 is a single-strand RNA coronavirus that enters human cells mainly by binding the angiotensin-converting enzyme 2 (ACE2) receptor.[7] ACE2 receptors are expressed in numerous tissues especially lung alveolar epithelial cells, the heart, kidneys, and the gastrointestinal tract.[7-9] The virus binds to ACE 2 as the host target cell receptor in synergy with the host's transmembrane serine protease 2 (cell surface protein). This leads to membrane fusion and releases the viral genome into the host cytoplasm.[7,8] Once inside cells, its RNA is released and transcribed mainly to nonstructural proteins. In the late phase, virus structural proteins are transcribed leading to viral assembly, maturation, and virus release.

COVID-19, MYOCARDIAL INJURY, AND CARDIAC ARRHYTHMIAS

The frequency of cardiac injury remains highly uncertain and confounded in current publications. Myocarditis is an uncommon pathologic diagnosis that occurs in 4.5% of highly se-

lected cases undergoing autopsy or endomyocardial biopsy.[10] The exact mechanisms by which COVID-19 causes myocardial injury are not clearly understood. A recent review suggested 2 mechanisms to explain injury to the heart: (1) direct entry of the virus into endothelial cells in the heart without necessarily entering myocytes and (2) hyperactivation of the immune system, characterised by the release of multiple inflammatory mediators, (such as interleukins, tumour necrosis factors and other inflammatory markers).[10] Inflammatory markers, such as leukocytes, C-reactive protein, and procalcitonin, have been detected in significantly elevated concentration among COVID-19 patients with cardiac injuries. These elevated levels of cytokines and inflammatory markers are associated with either apoptosis or necrosis of myocardial cells [11] At the moment, there is little evidence of COVID-19's direct impact in human cardiomyocytes; thus, the possibility of a direct myocardial infection from the virus remains to be confirmed and demonstrated.[12]

A second important issue associated with heart dysfunction is the occurrence of cardiac arrhythmia, most commonly in critically ill COVID-19 patients. Atrial fibrillation, atrial flutter, supraventricular tachycardia, complete heart block, cardiac arrest, and ventricular tachycardia may occur in patients infected with and recovering or recovered from COVID-19.[3] A recent systemic review including 1445 patients found cardiac arrhythmias were highly frequent in patients with COVID-19 and were observed in an average of 19.7% of study subjects (ranging from 11.7 to 27.6%).[3] According to early reports from China, higher arrhythmia rates (44%) were observed in patients with COVID-19 admitted to intensive care units (ICU).[13] The current literature lacks studies focusing on arrhythmias and the involved potential pathophysiological mechanisms. In most available reports, the specific causes of cardiac arrhythmias have not been elucidated, and it is difficult to distinguish between direct viral effects on the heart and arrhythmias caused by hypoxia and electrolyte abnormalities due to systemic illness and the exaggerated inflammatory syndrome or by medications. More focused data are required to better understand the pathophysiology of cardiac arrhythmias in COVID-19 patients and clarify the prevalence and the clinical impact of arrhythmias in asymptomatic, mildly ill, critically ill, and recovered patients.

COVID-19 AND STROKE

Stroke has emerged as a complication of COVID-19. SARS-Cov-2 can invade the blood brain barrier and survive by binding to ACE2 present in brain endothelial cells. Recent studies suggest SARS-CoV-2 enters the brain through axonal transport via the cribriform plate, adjacent to the olfactory bulb—thus the appearance of loss of smell as an early symptom of infection.[4] This process can lead to depletion of ACE2 in the brain cells and, in turn, over-activation of the classical renin-angiotensin system (RAS) axis. This over-activation decreases the activation of the alternative RAS pathway in the brain, resulting in an imbalance in vasodilation, neuroinflammation, oxidative stress, and thrombotic response. This imbalance is proposed to contribute to the pathophysiology of stroke during SARS-CoV-2 infection.[14] Findings after patient evaluation suggest that ischaemic stroke linked to COVID-19 infection, although not the main manifestation of the virus, can occur in the context of a systemic prothrombotic state, supporting the hypothesis that immediate prophylactic anticoagulation with low-molecular-weight heparins should be considered.[15] In a study among 214 patients with COVID-19, cases with severe infection based on respiratory status, had neurologic manifestations, such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]) and impaired consciousness (13 [14.8%] vs 3 [2.4%]) These patients were older and had more underlying disorders than those with less severe cases.[16] Furthermore, a meta-analysis of the literature published through May 2020 showed that among 39 studies reporting acute ischaemic stroke (AIS) occurrence, the pooled incidence of AIS in COVID-19 patients was 1.2% (54/4466) with a mean age of 63.4 ± 13.1 years and a mean duration of AIS from COVID-19 symptoms onset of 10 ± 8 days.[17] A high mortality rate of 38% (49/129) was also reported. The majority of AIS neuroimaging patterns showed large-vessel thrombosis, embolism, or stenosis (62.1%, 64/103), followed by multiple vascular territory (26.2%, 27/103).[17] In addition, elevated levels of dimerised plasmin fragment D (D-dimer) and fibrinogen and the presence of antiphospholipid antibodies were reported in laboratory exams of patients with concomitant AIS. [17]

COVID-19 AND COAGULOPATHY

COVID-19 infection is frequently accompanied by thrombotic complications and coagulopathy. COVID-19-associated coagulopathy (CAC), although partially overlapping in clinical and laboratory findings, has unique characteristics that differentiate from sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC), haemophagocytic syndrome (HPS) and haemophagocytic lymphohistiocytosis (HLH), antiphospholipid syndrome (APS), and thrombotic microangiopathy (TMA).[5] In comparison with bacterial-sepsis-associated coagulopathy/DIC, prolongation of prothrombin time, activated partial thromboplastin time, and decrease in antithrombin activity is less frequent, while thrombocytopenia is relatively uncommon in COVID-19.[18] In normal cells, ACE 2 converts angiotensin II to angiotensin, which stimulates endothelial cells to produce nitric oxide (NO). The production of NO encourages vasodilation and suppresses platelet aggregation.[5] In COVID-19 infection, SARS-CoV-2 occupies ACE2, thus allowing angiotensin II levels to increase, resulting in vasoconstriction and decrease in blood flow. Cell damage is aggravated, tissue factor expression upregulated, and protein C system downregulated. All these lead to coagulopathy and thrombotic events, with or without secondary complications (tissue hypoxia, concomitant infection).[19]

A consistent finding among COVID-19 patients is an elevated D-dimer count in the peripheral blood.[20] A study of 5700 patients in New York showed a median level of 438ng/ml (IQR: 262-872 ng/ml).[21] An increased incidence of arterial thromboses such as stroke and acute coronary syndromes has also been reported in COVID-19 cases after evaluation of 8910 patients in 169 hospitals around the globe.[22] In another study

among 183 patients, the overall mortality was 11.5%, non-survivors showed significantly higher D-dimer and fibrin degradation product (FDP) levels and longer prothrombin time and activated partial thromboplastin time on admission compared to survivors. According to the diagnostic criteria for DIC, 71.4% of non-survivors matched the grade of overt-DIC in later stages of novel COVID pneumonia, and only 1 survivor matched the criteria during the hospital stay.[23]

COVID-19 AND ARTERIAL THROMBOSIS

Thrombosis in patients with COVID-19 is most identified in the venous system but has also been reported in the arteries of the extremities and in cerebral, coronary, and visceral arteries. The pathophysiological mechanisms that explain thrombosis include inflammation, endothelial dysfunction, cytokine storm, coagulation disturbances, and hypoxia.[6,24] Various reports have described the occurrence of acute limb ischaemia at variable times during hospitalization, either isolated or in conjunction with thrombosis at other sites, predominantly associated with coagulation defects and increased D-dimer levels.[25-28]

Acute limb ischaemia is the most commonly occurring vascular disease requiring surgical treatment during the COVID-19 pandemic and is associated with a fourfold increased risk of death and a threefold increased risk of major adverse events.[44] Arterial thrombotic complications in patients with COVID-19 may present in a variety of ways. Acute upper limb ischaemia as the sole initial manifestation of COVID-19 infection, without concomitant respiratory symptoms or pneumonia, has been described.[40] Coagulopathy may lead to free floating thrombus in the aortic arch, the aortic bifurcation, and the iliac arteries.[27,42] Initial experiences from Italian institutions at the peak of the pandemic include instances of bilateral lower limb ischaemia secondary to acute aortoiliac thrombosis and acute upper left limb in patients with no comorbidities, atherosclerosis, atrial fibrillation, or pre-existing blood clotting disorders.[43] Interestingly, both patients at presentation were receiving low-molecular-weight heparin prophylaxis, and their D-dimer concentrations were higher than 9000 ng/mL. In addition, thrombosis of prior vascular reconstructions including stents and bypass grafts has also been reported.[29]

In a large case series, which included 49 confirmed COVID-19 patients with ischaemia, the distribution of ischaemic events was as follows: lower extremity, 71%; upper extremity, 14%; cerebral ischaemia, 10%; bowel ischaemia, 4%; and multiple locations, 12%; while concomitant deep vein thrombosis was observed in 16%.[30] Revascularization was performed in 27% and primary amputation in 10%, while 57% were treated with systemic anticoagulation only. The rate of limb loss was 18%, though 46% died in the hospital. In another study including 20 patients with ALI who were positive for COVID-19, revascularization was successful in 70.6%. In this study the use of prolonged systemic heparin improved surgical treatment efficacy, limb salvage, and overall survival.[31] Catheter-directed thrombolysis or open repair techniques for successful revascularization of the thrombosed arteries have been described.[30,31,42,43] Rates of successful revascularization in the existing literature vary; however, the rate of successful revascularization was, without doubt, lower than expected, and this reduced success rate was associated with a virus-related hypercoagulable state.[31]

GUIDELINES AND RECOMMENDATIONS ON USE OF ANTICOAGULATION IN COVID-19

Several international guidelines mainly based on consensus statements and expert opinions have been published on the use of anticoagulation in COVID-19.

The American Society of Haematology guideline panel suggests the use of prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19 related critical (patients who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or CCU) or acute illness (patients who require hospital admission without advanced clinical support in the ICU or CCU) who do not have suspected or confirmed VTE. [36,37] The Centers for Disease Control and Prevention (CDC) recommend that anticoagulants and antiplatelet therapy should not be initiated for the prevention of venous thromboembolism (VTE) or arterial thrombosis in non hospitalized patients with COVID-19. [37]

The CDC also recommends that therapeutic anticoagulation should be considered in clinically suspected thromboembolic events or high suspicion, despite of normal imaging findings.[37] The American College of Cardiology (ACC)[38] and the American College of Chest Physicians (ACCP)[39] recommend therapeutic anticoagulation in venous thromboembolism and patients with pulmonary embolism.

CONCLUSIONS

COVID-19 infection can impact the cardiovascular system, leading to complications that may negatively influence the outcome of affected patients. Cardiac complications include myocarditis, heart failure, and arrhythmias. The most important vascular complications include venous thrombosis, pulmonary embolism, acute limb ischaemia, stroke, and mesenteric ischaemia. Arterial thrombosis seems to be associated with coagulopathy and increased D-dimer concentrations and can manifest in patients with no pre-existing comorbidities, atherosclerosis, or blood-clotting disorders. The rate of successful revascularization is lower than expected and is associated with a virus-related hypercoagulable state.

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