Review
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Cardiac Diseases Following COVID-19 in Children and Adults: A Narrative Review on Mechanisms and Medical Implications

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Abstract

Objectives: In December 2019, SARS-CoV2 outbreak from China resulted in Covid-19 worldwide. The involvement of different organs, especially, heart disease can lead to hospitalization and enhance the rate of mortality and morbidity among severe patients. In a narrative review, we aimed to investigate the involvement of heart in adult and children with COVID-19 in critically ill patients.

Methods: The clinical and paraclinical manifestation of diseases in adults and children were searched in standard databases, such as PubMed, Google Scholar, Scopus, est. Also, the possible underlying mechanisms were investigated.

Results: The CVDs in COVID-19 patients has been characterized by several abnormalities such as myocarditis, acute myocardial injury, acute coronary syndrome, heart failure, arrhythmias, sudden cardiac arrest, coagulation abnormalities, thrombosis, and Kawasaki disease. The most probable mechanisms are attributed to SARS-CoV2 direct and indirect effects. The presence of angiotensin-converting enzyme 2 (ACE2) was confirmed in the cardiac tissue, confirming the direct attack of virus. Moreover, the cytokine storm as a result of enhanced levels of inflammatory mediators and infiltration of inflammatory cells into the cardiac disease, coagulation abnormalities, and endothelial dysfunction contribute to disease.

Conclusion: Cardiac diseases are seen in children and adults with COVID-19, related to the different mechanisms, mainly direct attack of virus and cytokine storm. Increasing the knowledge of cardiologists about the cardiac manifestations of COVID-9 in children and adults and underlying mechanisms can improve the consequences and reduce the mortality and morbidity rate among hospitalized patients.

Keywords: COVID-19, SARS-CoV2, cardiac diseases, ACE2, inflammation

Introduction

Generally, human coronaviruses (HCoVs) have been shown to be associated with mild disease. Novel emerged CoVs in China in 2002 (severe acute respiratory syndrome [SARS] pandemic) and Arabic Saudi in 2012 (Middle East respiratory syndrome [MERS] pandemic) reported to have a range of mild to severe manifestations which can lead to death.[1] Most recently, a novel virus outbreak of SARS-CoV-2 in December 2019 from China, lead to severe manifestations and death among coronavirus disease-2019 (Covid-19) patients.[2] As a beta-CoV subgroup,[3] SARS-CoV-2 can be transmitted rapidly among people due to its ability to be established in the air via aerosol and respiratory droplets.[4] Also, the particles of SARS-CoV2 (particularly RNA) was recognized in the stools of patients with COVID-19.[5] SARS-CoV-2 was reported to utilize angiotensin-converting enzyme 2 (ACE2) receptor to infect the targeted cells.[6]

According to literature, a wide range of symptoms from asymptomatic to severe has been reported for infected patients.[7] Additionally, 5% of COVID-19 patients have been reported to require to ICU, 2.3% need intubation with 1.4% mortality.[8] The mild to moderate symptoms of COVID-19 are similar to common cold in adults, including fever, dry cough, myalgia (fatigue), bronchiolitis, and pneumonia.[7] However, severe cases with multiorgan impartment have been observed.[9] The features of COVID-19 in paediatric patients are milder than adults.[10] The majority of paediatric patients (90%) were asymptomatic or exerted the mild to moderate symptoms. Severe symptoms and critical disease were seen in 5.8% of paediatric patients.[11]

COVID-19 can progress to acute respiratory distress syndrome (ARDS) and in addition to lung involves different organs and systems e.g., heart, liver, kidney, and gastrointestinal, hematological, and nervous system.[12] The severe disease has been predicted for patients with underlying condition, e.g., high blood pressure, diabetes, and cardiovascular diseases (CVDs), tumor, obesity, and chronic respiratory diseases.[13] CVDs, especially cute cardiac injury (8–12%), are one of the most common abnormalities among COVID-19 patients, associated with worse consequences.[14]

In this review, we reported the features of CVDs among children and adults with COVID-19 and possible mechanisms were described.

SARS-CoV-2 and ACE2

CoVs are generally an enveloped, very large, and positive-sense RNA virus.[15] Four structural proteins are translated form a part of genome, spike (S) glycoprotein, helical nucleocapsid (N), matrix (M), and small envelope (E) proteins.[16] Virus binds to binds to the ACE2 receptor via S-protein to enter into the host cells.[17] Similarities of SARS-CoV-2 genome to SARS-CoV (79.5%) shows that both use the same receptor to invade the host cells.[18] In SARS-CoV-2 structure the viral affinity to angiotensin-converting enzyme 2 (ACE2) increased.[19] S-protein of SARS-CoV-2 may bind to the host cell via ACE2 receptor and organs which express this receptor are more suspected to be

involved in COVID-19.[20] Thus, this receptor may play a critical role in development of COVID-19.[21] ACE2, a transmembrane protein with 805 amino acids, is an essential mediator of renin-angiotensin (Ang) system which negatively degrades Ang II to the heptapeptide Ang 1–7.[22] The presence of ACE2 receptor on different types of cells in human results in organ dysfunction in severe cases.[23]

COVID-19 Related Heart Diseases in Adults

The Manifestation of COVID-19 in the Cardiovascular System

COVID-19 has a high mortality rate which involved various parts of the body, including the lung as the primary target, heart, kidney, gastrointestinal, and nervous system.[24] Cardiovascular manifestations of COVID-19 include myocarditis, acute myocardial injury, acute coronary syndrome, heart failure, arrhythmias, sudden cardiac arrest, coagulation abnormalities, thrombosis, and Kawasaki disease.[25-28]

Myocardial Injury and Myocarditis

Acute cardiac injury is the most generally presented CV complication and it can result from direct myocardial injury, systemic inflammation, myocardial oxygen demand supply mismatch, acute coronary event, and iatrogenic.[29] Myocarditis is an inflammatory disease of the cardiac myocytes. Raised levels of cardiac biomarkers or anomalies of an electrocardiogram are the confirmations of acute myocardial injury which is reported in 7–20% of COVID-19 patients in Huang, Wang and Zhou studies.[30-32] Myocardial ischemia and myocardial necrosis can be detected by high-sensitive cardiac troponin I (hs-cTnI) as an important biomarker. Huang et al. in 2020 expressed the clinical aspects of 41 patients infected with COVID-19 and the results of their study showed that 5 patients had a myocardial injury with increased levels of hs-cTnI (>28 pg/ml), and 75% of patients were admitted to an ICU.[30] In Guo et al. study, the rates of death in COVID-19 patients just with the raised levels of hs-cTnI and in patients with underlying CVDs plus increased levels of cardiac troponin T were 37.5% and 69.4% respectively.[33] In addition to hs-cTnI, there are additionally several factors like aging, presence of comorbidities, and high levels of C- reactive protein which are the indicators of myocardial injury. In another study with 112 COVID-19 patients, it was found that 14 patients with a myocardial injury who had echocardiography abnormalities with raised levels of hs-cTnI didn't present the common indications of myocarditis like segmental wall motion abnormality or diminished left ventricular ejection fraction (LVEF) and based on these reasons, it was found that myocardial injury was secondary to systemic causes.[34] Inciardi et al. introduced the common signs of myocardial injury in a woman aged 53 years as raised levels of the biomarkers of heart, diffuse ST segment raise on the electrocardiogram, had diffuse biventricular hypokinesis on cardiac MRI, and also intensive LV dysfunction. In this case, the results of MRI showed some important features, including biventricular interstitial oedema, circumferential pericardial effusion, and increased diffuse late gadolinium.[35] Autopsy results in COVID-19 patients are not the same. For instance, the results of Xu et al. study[36] exhibited no proof of myocardial structural involvement but another case report demonstrated a patient with low-grade of inflammation of the heart and presence of coronavirus particles in the heart and these findings recommend that SARS- CoV-2 might infect the myocardium directly.[37] In Oudit study, the findings showed straight myocardial injury by the virus since the viral RNA was distinguished in 35% of the cardiac samples autopsied from human.[38]

Acute Coronary Syndrome

The acute coronary syndrome can result from the following mechanisms: plaque rupture because of inflammation/raised shear stress and exacerbation of pre-existing coronary artery disease.[29] In Bangalore et al. study 18 COVID-19 patients with ST segment elevation, as an indication of potential acute myocardial infarction, were assessed. 33% of patients had a myocardial infarction and 83% of them needed percutaneous coronary intervention.[39] In the Stefanini study, line with Bangalore study, 60% of COVID-19 patients with ST segment elevation showed the sign of a culprit lesion that required revascularization.[40] These findings introduced that COVID-19 can lead to acute coronary syndrome (ACS) by some events like plaque rupture, spasm of coronary, cytokine storm, or microthrombi resulted from systemic inflammation.[41,42]

Heart Failure

Based on the results of Chen et al. study, heart failure is one of the most generally identified complications of coronavirus and it was distinguished in 24% of all patients (49% of patients who died) and they announced the raised concentrations of amino-terminal pro-B-type natriuretic peptide in almost half of total cases (85% of those who died).[43] Another study demonstrated that failure of heart was announced in 23% of all cases (52% of patients who died).[32] Aging and pre-existing conditions like coronary artery disease, hypertension, and diabetes can intensify the failure of the heart in COVID-19 patients.[44] In addition to the conditions mentioned above, the response of the immune system to the COVID-19 infection can cause the advancement of cardiomyopathy and dysfunction of the myocardium.[45,46]

Arrhythmias and Sudden Cardiac Arrest

Direct tissue damage, hypoxia-mediated, and exacerbating coronary perfusion can prompt acute cardiac injury which is a reason for arrhythmia. It was reported that in the patients without fever or cough, the palpitation of the heart is the primary presenting indication of COVID-19.[47] Based on the results cohort study, cardiac arrhythmia was presented in 17% of 138 patients (44% of patients in the ICU).[48] The results of Guo et al. study exhibited that there was a connection between raised levels of troponin T and improvement of arrhythmias.[33] Another manifestation is sudden cardiac arrest which has been reported in COVID-19 patients both in hospital and out of hospital.[39,49]

Coagulation Abnormalities and Thrombosis

Raised concentrations of D-dimer, reduction in platelet numbers, and prolonged the prothrombin time (PT) are the instances of coagulation abnormalities, as one of the cardiovascular manifestations of COVID-19.[50] Raised levels of D-dimer were distinguished in 46% of all cases (60% of those with extreme sickness) in Guan et al. study.[51] The results of another study indicated that the levels of D-dimer were expanded (>1 mg/l) in 42% of all cases (81% of those who died) but just 5% of the patients had a low platelet count and also the PT was gentle even in patients with serious condition.[30] Clinical

observations exhibited that vein thrombosis and pulmonary embolism are usual complications in critically COVID-19 patients. The results of the autopsy in Wichmann et al. study revealed that the profound vein thrombosis and pulmonary embolism were identified in 7 and 4 patients of all 12 cases.[52]

COVID-19 Related Heart Diseases in Children

With lower incidence and milder COVID-19, paediatric patients also exerts lower incidence of severity 18.5%.[53] Severe symptoms including dyspnoea, central cyanosis, and an oxygen saturation <92%, as well as critical illness accompanied by respiratory failure, ARDS, shock, and multi-organ failure with abnormal coagulation, cardiac failure, and acute renal failure were associated with higher are of death among children.[11] Although most of the studies indicate that cardiac injury and acute myocarditis are important complications in adult COVID-19 patients, but in comparison with adults, pediatric patients showed a significantly lower prevalence of CVDs.[54] Some studies support this concept while presenting acute myocardial infarction and myocarditis in 6.4% of the children with age ≤10.[55] In addition to myocardial dysfunction, pericarditis and valvulitis have been reported in children's cardiac involvement.[56] Moreover, findings from one patient indicated a giant coronary aneurysm within a week of discharge from the pediatric intensive care unit.[57] In a case series of pediatric patients with COVID-19, chest radiographs and cardiac ultrasounds demonstrated a prominent cardiac area and mildly decreased left ventricular function respectively. The more achieved data from echocardiograms were related to the abnormalities such as diffused left ventricular hypokinesia (no segmental wall motion) abnormalities, respiratory collapsibility of the inferior vena cava, and decreased left ventricular ejection fraction.[58,59] The laboratory results in paediatric patients with COVID-19 also reported high levels of blood factors observed in myocardial injury following systemic inflammation, such as erythrocyte sedimentation rate (ESR), procalcitonin, C-reactive protein, interleukin (IL)-6, D-dimer, ferritin, troponin, triglycerides, and creatine kinase myocardial band, evidence of coagulopathy (by PT and partial thromboplastin time [PTT]).[57-59] COVID-19 can cause intensive inflammatory signs in a small ratio of paediatric patients.[54,60] Kawasaki disease has a well-known set of manifestation, including a persistent elevated fever, redness around the mouth, bloodshot eyes, redness and swelling of the hand and foot, and rash. A case series from the UK presented the hyperinflammatory syndrome with the features of Kawasaki disease in 62% of COVID-19 paediatric patients and a giant coronary aneurysm was identified by echocardiography in one patient.[57] However, there are some evidences that declare neither elevated myocardial enzymes nor signs of cardiac in children but mainly of findings indicated the significantly lower prevalence of comorbidities in the confirmed COVID-19 patients in children.

Mechanisms of SARS-CoV-2-Induced CVD

The potential mechanisms of SARS-CoV-2-induced CVDs are unknown. Two most potential mechanisms are direct attack of virus to the cells of cardiac tissue and higher levels of inflammation.[61] SARS-CoV2 can bind to the cells in cardiac tissue which expresses the ACE2 receptor, resulting in a direct myocardial involvement and myocarditis in critically ill patients.[62,63]

Direct Mechanism

The localization of ACE2 in heart, especially in endothelium and cardiomyocytes has been proven.[64] Other cells of cardiac tissue, such as epicardial adipose cells, pericytes, and cardiofibroblasts, as well as vascular structures, including smooth muscle cells, migratory angiogenic cells, and endothelial cells were reported to express this receptor. Therefore this evidence enhance the possibility of direct infection of cardiac tissue.[65] Similarly, SARS-CoV leads to myocardial infection via ACE2 in a murine model[38] and the direct inflammation of myocardium following SARS-CoV infection was recorded.[66] The presence of SARS-CoV-2 was confirmed in the autopsies of the heart tissue from a case of COVID-19.[67] In another study, the study of endomyocardial samples from non-ischaemic COVID-19 showed inflammation of interstitial tissue and endocarditis. The particles of virus were seen in the interstitial cells with damaged cell membrane however, the appearance of myocytes were normal without any viral particles,[68] confirming that SARSR-CoV-2 invades the interstitial cells. Additionally, the viral particles were detected in the cardiac endothelial cells in the electron microscopy findings.[69]

Indirect Mechanism

The cytokine storm as a results of inflammatory diseases is associated with cardiac injury.[70] Systemic inflammation following increased levels of cytokines, such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-6, and IL-8, as well as chemokines including CXC chemokine ligand (CXCL)-9, 10, and, 11 increase the risk of CVDs in COVID-19 patients.[71] Infiltration of inflammatory cells into the cardiac tissue and the overproduction of systemic inflammatory factors in COVID-19 causes apoptosis or necrosis of myocardial cells and subsequent myocardial infarction.[72,73] Also, the myocardial fibers swelling and of T helper cells presence were observed along with ultrastructural changes of cardiac tissue.[74] The systemic inflammation can be related to the dysfunction of endothelial, resulting in atherosclerosis which increases the risk of cardiac stroke.[75] Additionally, enhanced levels of cytokines causes the coronary microvasculature dysfunction and may lead to myocardial injury.[76] The elevated concentrations of proinflammatory cytokines also contribute to increasing the oxidative stress and reducing the endothelial nitric oxide synthase (eNOS), and lead to endothelial cell dysfunction and apoptosis.[77] Also, the raised levels of inflammatory factors also leads to the activated coagulation and microvascular thrombosis after SARS-CoV2 infection.[30] Therefore, SARS-COV-2 can induce cardiac dysfunction in COVID-19 patients.

Conclusion

Infection with SARS-CoV-2 leads to multiorgan dysfunctions and CVDs in adults and children, but the manifestation is milder and has lower rate death in paediatric patients. The main abnormality was acute cardiac injury in severe cases with COVID-19. Other cardiac manifestions include myocarditis, acute coronary syndrome, heart failure, arrhythmias, sudden cardiac arrest, coagulation abnormalities, thrombosis, and Kawasaki disease. According to the literature, COVID-19-realted CVDs in both adults and children may be associated with direct attack of virus which mainly related to the cardiac endothelial and interstitial cells of cardiac tissue. Moreover,

systemic inflammation and activated coagulation following SARS-CoV-2 infection via indirect mechanisms affects the cardiac tissue and leads to ultrastructural alterations, infiltration of leucocytes, endothelial dysfunction, and formation of vascular thrombosis, and results in cardiac manifestations. Thus, increasing the information of cardiologists about the cardiac manifestations of COVID-19 in adults and children, as well as the underlying mechanisms of SARS-CoV-2 induced CVDs can improve the management of this population and reduce the mortality and morbidity rate.

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