CARDIOVASCULAR COMPLICATIONS OF COVID-19

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ABSTRACT

The COVID-19 pandemic has seriously impacted health care delivery across the globe for obvious reasons. Although the virus mostly affects the respiratory system, manifestations in various other organ systems are not uncommon. The multiple cardiovascular complications of COVID-19 are mediated through various pathways. The presence of cardiovascular complications is more likely with pre-existing cardiac disease and presents with varying manifestations, many of which have an unclear pathophysiology. Management of these complications combines classical and novel treatment options with regard to known aspects of the pathophysiology of the disease and much hope lies in the development and effectiveness of new vaccines. This article summarizes the key cardiovascular complications, their known clinical features and the available treatment modalities according to existing data and knowledge.

INTRODUCTION

In 2019, an outbreak of pneumonia-like infections was reported in Wuhan, China. The infections were found to be caused by a novel Coronavirus, SARS-CoV-2 and soon spread rapidly across the globe. The disease caused by the virus was named COVID-19, and over a few months, it escalated to pandemic status and resulted in global shut-downs in an attempt to curb its spread. As of May 2022, the WHO has reported 521,920,560 confirmed cases of COVID-19, 6,274,323 of which have resulted in mortality.

The virus is highly contagious and patients commonly present with minor respiratory symptoms such as cough and fever. A minority of patients develop more severe symptoms leading to significant morbidity and mortality. Cardiac complications of the disease are prevalent and may be a pointer to poor prognosis among infected patients. As cited by Petrovic et al, the most common representations of cardiovascular complications of COVID-19 are seen as myocarditis, acute myocardial infarction, acute heart failure, arrhythmias, sub-clinical diastolic impairment and cardiac arrest.[1] In essence, COVID-19 is not just a disease of the respiratory system but results in an inflammatory response that can affect the cardiovascular system, making it necessary to achieve better understanding of these manifestations for the purpose of reducing morbidity and mortality.

EPIDEMIOLOGY

The novel enveloped RNA beta coronavirus infection has resulted in a pandemic that has infected over 510,270,667 individuals and caused over 6,233,526 deaths.[2] Insight into the cardiovascular complications of COVID-19 stems from preceding evidence that highlighted a strong association between severe acute respiratory syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS) and major adverse cardiovascular events such as myocardial infarction and sudden cardiac death.[3][4] SARS-CoV-2 virus affects the respiratory system primarily, however, cardiovascular complications of the viral infection, such as acute myocardial injury and myocarditis, cardiac fibrosis, arrhythmias and thrombotic event have been reported in infected individuals.[5][6][7][8][9]

These observations were further highlighted by reports of Huang et al, Ruan et al, and Yadav et al which revealed mortality from the infection were majorly attributed to respiratory failure and myocardial injury. This was found in 33% of 68 patients studied by Ruan et al. while Huang observed the incidence of acute cardiac injury ranged from 7.2% to 19.7% among the population studied [10] [11] [12].

PATHOPHYSIOLOGY

The SARS-CoV-2 virus, belonging to the Coronaviridae family and structurally and functionally similar to other members of Betacoronavirus Subgroup B, has been identified as being responsible for the development of COVID. [13] The virus is highly contagious and is easily transmitted via infected respiratory droplets. The virus is known to enter the host cells via ACE-2 receptor, which regulates the Renin Angiotensin Aldosterone System

(RAAS) and is important in maintaining haemodynamic stability and systemic vascular resistance. This receptor is known to mediate various pathways in cardiovascular physiology and pathology. [14] Another receptor that has been shown to be involved in the infectivity of COVID is the Notch receptor. The signaling pathway controlled by this receptor has also been implicated in other viral infections such as Yellow fever, Ebola and Avian influenza via the FURIN enzyme. The Notch pathway is also seen to play a role in hypoxic events that contribute to cardiovascular complications of COVID-19. Myocardial oxygen supply is compromised, leading to hypotension and in severe cases, shock. In addition, endothelial dysfunction leads to leaky cell junctions and extravasation of leukocytes from the blood to the tissues.[15]. This immune response to the viral infection also creates several inflammatory cytokines which activate the coagulation cascade and disrupt the normal balance between coagulation and primary fibrinolysis in the system. This results in what is known as *The Cytokine Storm Syndrome* which is attributed to vascular injury, myocarditis, arrhythmias and the destabilization of coronary artery plaques.

The COVID-19 virus and other members of the coronavirus family have been shown to cause myocarditis with several studies showing association between elevated troponin levels and mortality.[16]. Changes have been detected in the level of myocardial biomarkers such as creatine kinase. A study of 675 patients in China showed elevated LDH levels in 58.1% of severe cases. [17]

Arrhythmias have been known to occur in COVID infection via several mechanisms. There might be direct damage to myocardial cells and dysfunction of the conduction system. Previously existing myocardial conditions may also be worsened and aggravated by the infection. Electrolyte derangement and adrenergic stress lead to electrical instability and predispose to increased risk of cardiac arrest. A final possible mechanism is that which occurs in the presence of acute coronary syndrome leading to ischemia. Generally, the systemic inflammation resulting from the infection results in a proarrhythmic environment with undesirable influence on patient outcomes. [18]

The presence of heart failure and shock is another manifestation of COVID which is seen to be associated with poor prognosis. As with troponin, elevated levels of natriuretic peptide are associated with adverse outcomes in infected patients. Such onset can either be attributed to new onset or to exacerbation of existing cardiovascular disease.

Various factors have been associated with increased risk of cardiovascular complications. Underlying cardiovascular disease has been found to increase the risk of morbidity and mortality in those infected by the virus. Other factors found in association with underlying disease include age above 60 and male gender.[18] There was concern that in patients previously on ACE inhibitors and ARBs, upregulation of ACE-2 receptors might provide multiple binding sites for the virus. This has, however, not been clinically confirmed. It has also been proposed that an additional reason for increased risk of cardiovascular complications in long term COVID-19 infection is the immobility of patients during the period of illness and recovery. [19]

CLINICAL FEATURES

The cardiovascular complications of COVID-19 can range from asymptomatic myocardial injury with elevated cardiac biomarkers to sudden cardiac death. [20] Between these two are the spectrum of myocarditis, arrhythmias, coagulopathy, myocardial infarction and heart failure. [12] Myocarditis secondary to viral infection is significantly common and in most cases are asymptomatic, self-limiting and without sequelae [21]. This pattern was observed in COVID-19–related myocarditis. Nevertheless, symptomatic myocardial injury has also been reported. [22] Cardiac arrhythmias due to COVID-19 can be attributed to direct myocardial injury or secondary to a systemic hyperinflammatory state with hypercytokinemia and arrhythmogenic potential or both.[3] The study by Besler et al found that one of the pernicious resultant effects of ventricular arrhythmias associated with COVID-19 infection was sudden cardiac death. [23] Several determinants of prognosis have been identified, one of which is coagulopathy. This has been reported as an important predictor of poor prognosis in patients with COVID-19.[24] Prothrombin and activated partial thromboplastin times were prolonged in non-survivors. Also, there were observations of significantly elevated D-Dimers and other fibrin degradation products in those who did not survive compared to those who did. [25] The coagulopathy observed in COVID-19 which is worsened by severe inflammatory response and hypoxia tilt haemostasis towards thromboembolic events. [26] Heart failure in patients with COVID-19 can range from mild heart failure with preserved ejection fraction in the early stages of the illness to severe end-stage heart failure and cardiogenic shock with increased mortality. [27] This can be due to direct myocardial injury or precipitated by the inflammatory response of the body. [2]

MANAGEMENT

Of great importance is identifying promptly the early signs of onset of heart failure. Causes of decompensation should be identified and immediately corrected and managed to avoid adverse outcomes. Hypoxemia is worsened in this group of patients and thus, oxygen therapy and mechanical

ventilation should be applied even more so in patients with heart failure and other cardiovascular manifestations. Because pulmonary edema following rapid fluid resuscitation will further impair alveolar reventilation, rehydration should be carefully prescribed in shock due to COVID-19 as compared to other causes of shock. Pharmacological treatment options were initially modeled against the few known pathways of the disease process. Given the link between increased ACE-2 expression and cardiovascular morbidity, several cardiological societies have recommended the use of ACE inhibitors and ARBs to antagonize the receptors. [14] Of added benefit are the anti-inflammatory properties of these medications. For patients who already suffer cardiovascular diseases related to high levels of LDL and total cholesterol, continuation of statins while on treatment has been associated with reduced ICU admission and disease severity. [18] Although there is no general agreement for the management of myocarditis, antiviral therapy (lopinavir-ritonavir) and steroids have been found useful in improving outcomes. They must however be administered with caution because interaction with class IA and III antiarrhythmics may cause QTc prolongation. They also alter drug concentrations of clopidogrel, ticagrelor and direct inhibitors of Xa and IIa. In addition, direct lopinavir-ritonavir association can directly cause hypotension and atrioventricular conduction disturbances. Possible vaccine options also include targeting the viral S-protein which reduces the binding capacity and efficiency index of the enzyme. Other promising options, though with less evidence for justification are the use of convalescent plasma containing antibodies which in theory, make scientific sense.

CONCLUSION

There have been great efforts directed at combating COVID-19 through prevention by lockdowns and vaccination and improving the approach to management, however, the emergence of different strains has enhanced the persistence of this global pandemic. The viral infection remains highly contagious and its cardiovascular complications range from asymptomatic to lethal. Myocardial injury and heart failure have been identified as the main cardiovascular causes of death in infected patients. The prompt diagnosis of these complications by assessment of cardiac biomarkers and appropriate initiation of management as highlighted in the article will help to prevent lethal outcomes and overall improve the survival rate of the patients.

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