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COVID-19: Cardiopathy, Vasculopathy and Coagulopathy

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ABSTRACT

Late in 2019 a newly discovered coronavirus appeared in China. Later, this coronavirus was called severe acute respiratory syndrome coronavirus-2 (SARC-CoV-2). Infection with this virus leads to a clinical condition known as coronavirus disease-2019 (COVID-19). As of 20th December 2020, the highly contagious virus has spread worldwide with more than 78 million positive cases and 1.7 million confirmed deaths. Presently there is no medication to cure COVID-19 due to the lack of knowledge of the pathophysiology of this clinical disorder. As a result, extensive work has to be done to reveal its pathophysiology. Although COVID-19 clinical manifestations are mostly pulmonary, major cardiovascular complications have been described. Studies revealed that COVID-19 exacerbates the clinical conditions in patients with cardiovascular diseases. The mortality rate due to COVID-19 is significantly associated with comorbidity especially those with preexisting cardiovascular diseases. Cardiovascular abnormalities are not only prevalent but also predictive. Several cardiovascular diseases have been observed in patients with COVID-19 such as cardiac injury, arrhythmia, heart failure, endothelial inflammation, coronary artery disease and thrombosis. This review article presents evidence that COVID-19 is associated with cardiopathy, vasculopathy and coagulopathy.

1. Introduction

Since it started in Wuhan in China in December 2019 until this moment, the world is still confronting the pandemic of COVID-19 (1) . Since then, the health care system around the world is passing through a real-time learning process. While the pandemic continues, an enormous wave of data has been published by the scientific journals. Although COVID-19 clinical presentations mostly affect the pulmonary system, other complications such as cardiac, renal (2), hepatic (3), and neuronal (4) complications have been described. Cardiovascular involvement in COVID-19 has been reported at the level of the heart and in the vascular beds. COVID-19 does not only have a significant impact on patients with preexisting cardiovascular co-morbidity, it also has direct impact on the cardiovascular system (CVS) more widely. Several conditions have been reported such as cardiac injury, myocarditis, arrhythmia, heart failure, vasculopathy and coagulopathy. This review aims to present the available evidence for the occurrence of these conditions in COVID-19.

2. Cardiac injury

Cardiac injury (CI) is frequently amongst COVID-19 patients and is associated with a greater risk of mortality. A study of 416 patients showed that 19.7% had CI with an abnormal increase in Troponin I (TnI) and other cardiac biomarkers such as creatinine kinase-myocardial band (CK-MB) and N-terminal pro-B-type Natriuretic peptide (NT-proBNP) (5). Cardiac dysfunction appears to be a distinct feature of COVID-19 in up to one third of the hospitalized cases. Cardiac damage and heart failure (HR) may contribute to 40% of mortalities (6). The clinical features of 41 patients admitted to hospital in Wuhan showed that 12% of patients had acute CI with increased TnI (7).

In a study of cardiovascular complications in 187 patients, 28% presented with a myocardial injury and a significant rise in Troponin T (TnT). The mortality rate in patients with elevated TnT was higher (59.6%) as compared to those with normal TnT (8.9%) (8). Moreover, in a study of 191 patients, 17% (46% of the non-survival group) found to have increased TnI level, and 23% (52% of the non-survival group) had cardiac failure (9). Furthermore, 23% of 52 critically ill COVID-19 patients in the ICU had a cardiac injury with elevated TnI (10). Moreover, in a study of 120 patients, significant increases in NT-proBNP and TnT were observed among 28% and 10% of the patients respectively. Interleukin-6 (IL-6) was also dramatically increased. The hyperinflammation observed might be the basis behind the etiology of fulminant myocarditis (11). Myocardial injury is associated with a reduced survival rate and might be an important prognostic factor of COVID-19 (12). Thus, cardiac abnormalities in COVID-19 patients are not only prevalent but also predictive.

The mechanisms of cardiomyopathy with the subsequent elevation of cardiac biomarkers in COVID-19 are yet to be identified. Several mechanisms have been suggested including direct myocardial damage by SARS-CoV-2 invasion leading to myocarditis, or indirect due to myocardial stress developed from vasculopathy, coagulopathy, respiratory failure, hypoxemia, cytokine storm, or may be a combination of some or all of these mechanisms. The presence of a viral entry receptor in the heart and vessels suggests an intrinsic susceptibility to SARS-CoV-2 infection. Recent autopsy studies revealed that SARS-CoV-2 RNA and viral bodies were detected in multi-organs including the heart, blood vessels, lung, liver, and kidney of COVID-19 patients (13,14). Moreover, the SARS-CoV-2 invasion of endothelial cells was evident by the presence of viral bodies in the endothelial cells of multiple organs such as the heart and the lung (15). These findings suggest the probability of the stimulation of local downstream signaling pathways in the cardiac and vascular cells leading to a robust immune response with cell injury and lysis. Several molecular targets have been identified for SARS-CoV-2 including angiotensin converting enzyme 2 (ACE2) (16) and CD147 (17). However, their direct role in COVID-19 associated cardiovascular disease (CVD) remains unclear.

Myocarditis is currently known as a complication of COVID-19. However, its pathophysiology remains elusive. Myocarditis is an inflammatory disease of the cardiac myocytes that results from infectious and non-infectious disorders. Several mechanisms could explain COVID-19-induced myocarditis. First, immune-induced

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myocarditis, in which innate and acquired immune reactions involving CD4+ and CD8+ T-lymphocytes activation, leads to cardiac damage and subsequently dilated cardiomyopathy (18,19). Although T-cells contribute to host immune response through inhibition of viral replication, they may also stimulate cardiac damage through over-activation of cytokines, leading to cellular cytotoxicity (18). The second proposed mechanism is autoimmune-induced myocarditis that results from the release of cryptic antigens, cardiac myosin and other unrecognized proteins on the surface of myocardial cells leading to the stimulation of adverse autoimmune responses (20). Third and finally, myocarditis could also result from direct invasion of SARS-CoV-2 to the components of the immune system, followed by replication and creation of viral proteins, leading to myocardial cells apoptosis, necrosis and eventually cardiac injury (21,22). However, whether one or more or none of these mechanisms causes myocarditis in COVID-19, extensive research is needed to explore the exact mechanism involved in cardiac injury.

3. Arrhythmias

Another facet of CVD involvement is the disturbance of cardiac electrophysiology. In a report on 138 COVID-19 patients, arrhythmias occurred in 17% of these patients. This comprised 44% of the ICU cases and 7% of non-ICU suggesting that critically ill cases often have complications disturbing cardiac electrophysiology (23). However, the study did not determine the type of arrhythmia. In a retrospective study characterizing the clinical features of 137 COVID-19 patients, 7.3% of the total cases presented with clinical manifestations including heart palpitations (24). Another retrospective study on 187 patients exhibited that 27.8% of the cases had myocardial injury with increased level of TnT. Those patients had frequent malignant arrhythmias including ventricular tachycardia and fibrillation (8). In addition to other complications, 23.5% and 14·7% of 34 patients had arrhythmia and acute cardiac injury respectively (25). In a retrospective study of 85 patients with SARS-CoV-2 infection, 60% of the cases had arrhythmia (26). Another study of 700 patients with COVID-19 showed different incidence rates of arrhythmia associated with ICU admission, such as 9 cardiac arrests, 25 atrial fibrillation events, 9 incidents of brady-arrhythmias, and 10 non-sustained ventricular tachycardia (27). These studies indicate that arrhythmia is common among COVID-19 patient.

The mechanism by which COVID-19 causes arrhythmia is not totally understood. Recent report showed that COVID-19 is associated with sinus node dysfunction (28). Myocardial inflammation or direct viral infiltration are possible mechanisms behind sinus node dysfunction. A case study of a young adult presented evidence of prevalent pathophysiological disturbance of the cardiac conductive system including sinus node dysfunction, atrioventricular node dysfunction, and interventricular conduction block. The authors speculated that SARS-CoV-2 injures the cardiac conduction system, including the Purkinje cells, even without evident respiratory damage (29).

Currently there is not sufficient evidence to explain the mechanism through which COVID-19 causes arrhythmia. However, arrhythmia could occur secondary to lung injury causing hypoxemia and an unstable status of myocardial electrical and conductive system damage. Arrhythmia could also occur as a result of deterioration of pre-existing myocardial illnesses, or conduction disturbances. COVID-19 might cause severe anxiety triggering catecholamine release and subsequently myocardial electrical instability (30). In addition, hyperinflammation and myocarditis could potentiate arrhythmia in COVID-19 patients (31).

Cardiac injury due to myocarditis is common among critically ill COVID-19 patients. Viral-induced myocarditis are thought to cause arrhythmia through the interaction between the viral components and host cells. This interaction leads to intercellular coupling, accumulation of fluid in the interstitial space, fibrosis of the myocardial tissues leading to defect in the cardiac conduction system. This results in anomalous calcium ion handling and downregulation of potassium ion channels leading to abnormal action potential of cardiac myocytes (32). Viral induced myocarditis is associated with ion channel malfunction and electrophysiological disturbance leading to arrhythmia (33). Hyperpolarization of the resting membrane potential of the cardiac myocyte in an animal model of viral myocarditis has been reported (34). Atrial fibrillation is common among COVID-19 patients (35). A previous report on viral induced atrial fibrillation showed elevation of IL-1β, TNF-α, IFN-γ, IL-9, G-CSF, and GM-CSF (36). Elevated cytokines also occur in COVID-19 and may explain the inflammation in the conduction system leading to arrhythmias. In addition to hyperinflammation and myocarditis, arrhythmias could result from treatment side effects (37), overactivation of protein kinase C and activation of oxidized Ca^{2+}/calmodulin-dependent protein kinase II (38).

Currently, the available data lacks specific focus on arrhythmias and their potential mechanisms in COVID-19. This makes it challenging to differentiate between arrhythmias caused by hypoxia, metabolic disorders, proinflammatory cytokine storm, medication and direct viral attack of cardiac myocytes. This ambiguity suggests further research is required to explore the mechanisms leading to arrhythmias in COVID-19.

4. Heart failure (HF)

COVID-19 could have a detrimental effect on the heart particularly on patients with underlying CVD. A nationwide study in China on 1590 hospitalized patients with COVID-19, revealed that patients with CVD with/without risk factors for CVD were more predisposed to HF. In relation to CVD, HF was the third most common comorbidity and was more evident in severe cases (33.9%) as compared to non-severe cases (15.3%) (39). Another study supported this finding, where the frequency of HF was prominent among non-survivors (52%) in comparison to survivors (12%) (9). Elevated HF biomarker, brain-type natriuretic peptide (BNP), is common among critically-ill COVID-19 patients. Among 21 COVID-19 patients admitted to ICU, 43% of them had heart failure as a co-morbid condition (40). A retrospective study on the clinical features of 113 COVID-19 non-survivors revealed that 77% and 41.8% had acute cardiac injury and heart failure respectively (41). The investigators found that cases with pre-existing CVD were more susceptible to exacerbation of heart complications and that acute CI and HF were more common regardless of their disease history. These findings indicate that heart failure is common among COVID-19 patients either as a comorbid disorder or even as a cause of death among critically ill patients. The data are also consistent with previous finding, where SARS-CoV-2 caused left ventricular dysfunction with the damage more prominent in critically ill patients (42).

With regard to the effect of COVID-19 on the left ventricular function, data from 39 patients admitted to ICU and who underwent transthoracic echocardiography examinations showed that left ventricular ejection fraction (LVEF) was significantly lower in patients who underwent intubation or died (51.2%) as compared to survivors without intubation (61%). The data suggest that reduced LVEF might be an additional risk marker in COVID-19 (43). This prognostic finding is supported by a study on 75 patients which revealed that the lower the ejection fraction the higher the mortality rate among COVID-19 patients (44). Left ventricular global longitudinal strain (LVGLS), which measures the maximal shortening of myocardial longitudinal length during systole compared to the resting length in diastole, was reduced (45) and this ratio was also associated with mortality in COVID-19 patients (46). However, multiple factors could affect the severity of the disease and the mortality rate in different populations, such as patient age, ethnicity, genetic variations, stage of disease, comorbidity, medical facilities and cultural variations such as alcohol consumption and diet style.

The mechanism by which COVID-19 causes HF is not fully understood. Some viral infection can severely disturb the heart leading to acute coronary syndrome, cardiac injury, myocarditis, arrhythmia and eventually HF (47). These complications are more likely to develop in patients with pre-existing CVD. They could result through direct SARS-CoV-2 invasion of the cardiac tissues or may be through a systemic response, such as microvascular dysfunction, hyperinflammation, immune response or aggravated hypoxia. The molecular mechanism by which COVID-19 leads to HF is largely unknown. SARS-CoV-2 invades the host cells through multiple receptors such as ACE2 and CD147. These receptors could activate downstream pathways leading to cardiac dysfunction. Currently there is no direct evidence to support the responsibility of ACE2 and CD147 receptors in the pathogenesis of HF in COVID-19.

COVID-19 is associated with cytokines storms particularly among critically ill patients. Hyperinflammation could be the cause behind the failing heart. A typical inflammatory response involves four elements (48): first, the inflammatory inducers (SARS-CoV-2).

Second, the sensors that detect the inflammatory inducer such as ACE2 and CD147. Third, the inflammatory mediators induced by those sensors such as IL-1β, IL-2, IL-6, IL-7, IL-8 and TNF-α (7). Forth and final, the target cells that are attacked by those mediators such as cardiomyocytes, endothelial cells, immune cells and platelets. HF is associated with high level of IL-1ß, IL-6 and TNF-α. The latter has a strong correlation with the severity of HF (49). IL-1ß, IL-6 and TNF-α affect intracellular calcium homeostasis in cardiac myocytes through decreasing the expression of sarcoplasmic reticulum Ca^{2+}-ATPase, Ca^{2+} release channel and voltage-dependent Ca^{2+} channel causing a negative inotropic effect (50) (51). TNF-α and IL-1ß promote myocardial hypertrophy, apoptosis and pyroptosis (52). IL-6 promotes myocardial fibrosis, hypertrophy and stiffness (53). These observations indicate that hyperinflammation associated with COVID-19 could lead to HF. However, the relationship between inflammation and HF is complicated and often interrelated and are mutually reinforcing. Inflammation could be the cause and consequence of HF (52).

COVID-19 is also associated with microvascular dysfunction that will be discussed later. Mounting evidence indicates that microangiopathy is a key determinant of the pathological process of HF (54). The high burden of comorbidities including diabetes, hypertension, chronic kidney disease could augment the systemic inflammatory status (as proposed by the rise of IL-1RL1, IL-6, CRP, TNF-α, pentraxin-3 and others) that affects endothelial function, thereby affecting several pathophysiological pathways (such as downregulation of NO-cGMP pathway, upregulation of oxidative stress status) and eventually leads to myocardial fibrosis, stiffening and dysfunction (54). To support the significance of microangiopathy in HF, a connection between parvovirus infection of endothelial cells and left ventricular diastolic dysfunction has been observed (55). Taken together, HF is common among COVID-19 patients, and more prominent among critically ill patients particularly those with underlying CVD. Multiple mechanisms have been proposed but none of them have been proven in the settings of COVID-19. However, anti-inflammatory medication should be considered during the clinical care of those patients.

5. Vasculopathy and Coagulopathy

Accumulating evidence exhibited that COVID-19 is associated with vasculopathy and coagulopathy, with increasing morbidity and mortality due to thrombotic complications. Vasculopathy and coagulopathy seem to be interrelated in COVID-19. The involvement of endothelial cell pathology throughout the vasculature of various organs has been reported. Postmortem analysis using electron microscopy revealed viral inclusion structures in endothelial cells causing prominent endotheliitis, suggesting the invasion of the vasculature by SARS-CoV-2 (15) (56). This invasion induces inflammation leading to vascular injury and leakage, which triggers the release of exuberant pro-inflammatory cytokines (57-59). Vascular injury of the cardiac tissues causes perfusion dysfunctions, vascular hyperpermeability and narrowing, leading to CI and elevation in troponins (60). These observations pave the way to a better understanding of the pathogenesis of vasculopathy and cardiopathy in COVID-19. Endothelial dysfunction could also explain the prevalence of hypertension (31%) as the most common co-morbid disease and represents 58% among critically ill patients admitted to ICU (39) (23).

It is well known that the endothelium plays a crucial role as a paracrine, endocrine, and autocrine organ. It regulates vascular tone and maintains vascular homoeostasis. Its dysfunction is the main determinant of microcirculation dysfunction leading to a pro-adhesive and procoagulant status. It inhibits clot formation through keeping an antithrombotic surface, producing tissue factor inhibitor and by expressing tissue-type plasminogen activator (t-PA) that stimulates blood clot degradation (61). Therefore a disturbance in endothelial function may lead to coagulation disorders. Coagulopathy in COVID-19 patients has been reported in multiple organs such as the lung, heart, blood vessels and brain indicating the widespread nature of thrombotic complications (62). Prominently raised levels of D-dimer, upper normal fibrinogen levels, modest reduction in platelet count and prolonged prothrombin time are common laboratory findings in COVID-19 patients. Elevated levels of D-dimer are strongly correlated with the severity of the disease and the risk of thrombosis (63) (7). In a retrospective study describing the coagulation features in 183 patients with COVID-19, the prothrombin time and the mean level of D-dimer were significantly higher in non-survival patients (2·12 mg/L; range 0·77–5·27) as compared to the survivals (0·61 mg/L; range 0·35–1·29) (64). A similar finding by Huang et al. indicated that ICU patients had considerably elevated median D-dimer (2·4 mg/L, range 0·6–14·4) as compared to non-ICU patients (0·5 mg/L, range 0·3–0·8) (7). Another retrospective study of 449 severely ill patients, the mortality rate was associated with the level of D-dimer and prothrombin time, however treatment with heparin significantly reduced the mortality rate (63). Moreover, postmortem findings revealed microvascular thrombotic accumulations in small vessels of multiple organ systems (62). Collectively, thrombosis is common among COVID-19 patients making them vulnerable to various CVD events.

Like other infections, a significant portion of COVID-19 patients present with coagulation abnormalities such as disseminated intravascular coagulation; venous and atrial thrombotic microangiopathy; pulmonary embolism and cardiac complications. The difference in COVID-19 patients is that such abnormalities are associated with high risk of mortality (62). In a study in 184 ICU patients with positive SARS-CoV-2, 31% of them presented with thrombotic complications such as venous thromboembolism (27%), arterial thrombotic events (3.7%) and most frequently pulmonary embolism (81%) (65). In a cross-sectional study in Wuhan, the incidence of deep vein thrombosis (DVT) was extremely high (85.4%) among critically ill patients (66). Autopsy obtained from 12 patients with COVID-19 revealed DVT in 58% of them, of whom 33% died from pulmonary embolism (13). Cases of coronary thrombosis, cerebral venous sinus thrombosis and arterial mesenteric thrombosis have all been reported among COVID-19 patients (67). Taken together, these evidences suggest that COVID-19 is associated with widespread thrombosis with subsequent detrimental effect on cardiovascular system, supporting the recommendation of rigorous application of thrombosis prophylaxis in all critically ill patients.

The exact mechanism by which thrombosis occurs in COVID-19 is largely unknown. Thrombotic microangiopathy is obviously caused by interactions between platelets, endothelial cells, and leukocytes. Multiple factors such as CD147, ACE2, P-selectin, P2Y12 receptor, protein arginine deiminases 4, and von Willebrand factor, are attractive targets to block cellular thrombi-inflammatory interactions (68,69). However, currently, there is no direct evidence to support the role of these factors in SARS-CoV-2 induced thrombotic complication. COVID-19 is associated with the release of pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α. IL-6 can stimulate tissue factor expression in leukocytes, which triggers coagulation and thrombin generation. IL-6 stimulates the coagulation factors and vascular endothelial cells but suppress cardiac muscle activities (70). Cytokines such as TNF-α and interleukins stimulate the extrinsic coagulation pathway and impede fibrinolysis (71). It has also been reported that SARS-CoV-1 leads to the over-activation of a wide range of genes involved in both intrinsic and extrinsic coagulation pathways such as fibrinogen, prothrombin, thromboplastin, stable factor, factor X, XI and XII. Over expression of serine proteinase inhibitors and platelet aggregation factors such as TBXAS and TLR9 have also been reported (72). If that is the case with SARS-CoV-2, activation of coagulation cascades and genes over-expression of coagulation factors could explain the hypercoagulability and thrombosis observed in COVID-19. IL-17A contribute to the pathophysiology of CVD associated with immunological disorders. A recent study revealed the possible contribution of IL-17A in relation to coagulopathy and vasculopathy in COVID-19 patients (73). Moreover, TNF-α and IL-1 are key factors that suppress the endogenous anticoagulant pathways. Long term treatment with anticoagulants suppresses the expression of IL-1, IL-6 and TNF-α (74). Furthermore, the plasma level of t-PA is much higher in SARS-CoV-1 positive patients (75). Inflammation-induced endothelial cell injury could result in enormous discharges of t-PA which could explain the high level of D-dimer and fibrin degradation products in patients with severe COVID-19.

Another emerging mechanism of vascular injury and thrombosis in COVID-19 is the activation of complement pathways. In pulmonary microvasculature, a recent finding from 5 cases with COVID-19 revealed deposition of complementary components such as membrane

attack complex (C5b-9), split C4 complement component (C4d) and mannose binding lectin (MBL)-associated serine protease. In some cases, co-localization of SARS-CoV-2 spike proteins with C4d and C5b-9 were observed (76). The possible involvement of complementary pathways in the pathophysiology of COVID-19 is supported by previous findings in animal models. The severity of SARS was significantly reduced in the murine model lacking C3, a key activator of common complement pathway (77). Moreover, severity of MERS was significantly decreased and the cytokine response was reduced by targeting C5a with specific antibody (78). Whether complement inhibition is a promising therapy for COVID-19 associated angiopathy and thrombosis, the mentioned report may provide a basis for the further investigation of the pathophysiology of complement in COVID-19. Taken together, COVID-19 is associated with vasculopathy and coagulopathy aggravating cardiac and vascular injury and predisposing the patient to multiple organ failure.

6. Conclusion

Although COVID-19 is a respiratory disease, the burden of the disease reaches other organs such as the organs in the cardiovascular system. Patients with pre-existing cardiovascular co-morbidity or risk factors are more susceptible to COVID-19 complications. The mechanism by which COVID-19 causes cardiopathy, vasculopathy and coagulopathy is still unknown. However, findings of viral bodies in the cardiovascular myocytes imply direct invasion by SARS-CoV-2. Viral invasion could modify downstream signaling pathways leading to cellular dysfunction, inflammation and injury. However, the direct invasion remains inconclusive due to a limited number of studies. Further studies are undoubtedly required to explore the exact mechanisms by which COVID-19 causes various cardiovascular manifestations.

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