Microvascular Angiopathic Consequences of COVID-19

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Abstract

The coronavirus disease-2019 (COVID-19) pandemic has rapidly spread across the world. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first appeared in Wuhan, China in December, 2019. Ever increasing data is emerging about the impact of COVID-19 on cardiovascular tissue. Clinical features associated with COVID-19 suggest that endothelial cell dysfunction and microvascular thrombosis are to a large part contributing to resultant multi-organ complications. This review is aimed at highlighting the critical aspects associated with COVID-19 and its presumed microvascular angiopathic consequences on the cardiovascular system leading to multi-organ dysfunction.

Introduction

Coronaviruses (CoVs) are enveloped, non-segmented, single strand positive sense RNA viruses that are widely distributed among humans and other mammals. This group of viruses belongs to the coronaviridae family of viruses, and are harbored in animals such as civets, dogs, cats, bats, and camels.[1-3] To-date there are six coronaviruses (CoVs) known to infect humans and these include; 229E, OC43, NL63, HKU1, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV).[1, 3, 4] The 2002-2003 pandemic in Guangdong, Southern China was caused by SARS-CoV-1,[5] and resulted in >8000 human infections, and 774 deaths in 37 countries.[6] More recently in 2012 and 2015, MERS-CoV was responsible for the outbreaks that caused nearly 2,500 infections, and >850 deaths.[7 8] Although another CoV outbreak was predicted by various organizations, the scale of a resultant global pandemic was not completely anticipated.

The coronavirus disease-2019 (COVID-19) is a novel emerging infectious disease that is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 was declared a global pandemic by the World Health Organization on March 11th, 2020.[9] This viral disease first appeared in Wuhan, Hubei province, China in December 2019. According to the Johns Hopkins University Coronavirus resource center dashboard, for instance on September 3rd, 2020, the disease has been confirmed in 188 countries, infected >26 million individuals, and caused >800,000 deaths.[10] In the US alone there were >6 million confirmed cases, and > 180,000 deaths.[10]

Like other SARS-CoV, COVID-19 can cause a severe pulmonary viral pneumonia leading to severe hypoxia and subsequent respiratory failure. However, emerging evidence demonstrates that unlike the majority of respiratory viral illness, COVID-19 can also lead to

cardiovascular and multi-organ complications.[11-13] Although the basic biological understanding of these complications is currently unknown, there is some evidence to suggest that COVID-19 can cause microvascular angiopathy in multiple organ and tissue beds.[14, 15]

Basic Biology

The SARS-CoV2 has been reported to bind to angiotensin converting enzyme 2 (ACE2) protein.[16] Specifically, it was determined that it is the S1 domain of the SARS-CoV S protein that binds effectively and efficiently to the ACE protein on cells.[16] The ACE protein therefore acts as the attachment and entry site for the virus into mammalian cells (**Figure 1**). It was further determined that the ACE2 antibodies blocked viral replication, but not ACE1 antibodies[16]. These data demonstrated convincingly that ACE2 is the functional receptor for SARS-CoV.

Upon binding onto the cell membrane ACE2 protein, the SARS-CoV2 virus enters the cell via a receptor mediated endocytosis and uses the host cell nuclear machinery to replicate,[17] which produces many virion triggering an inflammatory response leading to production of cytokines including but not limited to Interleukin-1beta (L-1β), interferon gamma (IFN-γ), and Monocyte Chemoattractant Protein-1 (MCP-1) (**Figure 1**). The chemokine (C-C mofit) ligand 2 (CCL2) also known as MCP-1 binds to its receptor on the surface of the microvascular ECs cells and pro-inflammatory macrophages, [18, 19] further triggering more cytokine release and recruitment of immune-inflammatory cells. The resultant release of additional cytokines leads to a severe cytokine storm, which causes significant cellular and tissue damage. [18]

The ACE2 mRNA is detectable in virtually all mammalian tissue, however, the protein is most remarkably expressed on the cell surface of lung alveolar epithelial cells and intestinal

enterocytes.[17] The protein is also highly expressed on the arterial and venous endothelium.[17] Given the abundance of ACE2 on the cell surface of endothelial cells, prior to the COVID-19 pandemic it was speculated that SARS-CoV-2 viruses can lead to vascular dysfunction, endothelial cell damage, and microvascular thrombosis.[15, 20]

Microvascular Angiopathy

Microvascular angiopathy is a pathological sequelae of a multitude of conditions that result as a consequence of over-activation of host immune defense mechanisms. Among patients impacted by sepsis or septic shock from a bacterial, viral or autoimmune processes, this hyperimmune response can be as, if not more, devastating to the host as the initial infectious etiology.[21-25] For example, dengue viral infections can cause a host to mount a hyperimmune response leading to a severe cytokine storm.[23, 24] This unleashes activation of M1 macrophages, and the release of pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6.[23] These factors directly act on the endothelium leading to cellular dysfunction, increased vascular leakage, and increased microvascular thrombosis. As a consequence patients present with clinical manifestations of multi-organ dysfunction such as severe adult respiratory distress syndrome, myocarditis, acute kidney injury as well as skin changes such as petechiae, bruising, and purpura.[23] Bacterial infections such as Lyme disease (*Borrelia burgdorferi*) and Rocky Mountain spotted fever (RMSF; caused by *Rickettsia rickettsii*) also can lead to severe cytokine storm, overexpression of CCL2, and resultant microvascular injury. In presence of such infections, patients often develop microvascular dysfunction and thrombosis, as well as over-activation of the host fibrinolytic system.[21, 22, 25, 26]

Prior literature establishes a clear interplay between inflammation, hypercoagulation, and thrombosis. Cytokine storm causes a higher propensity to the development of disseminated intravascular coagulopathy (DIC).[27] The widespread activation of the coagulation pathway by cytokines generates a prothrombotic state characterized by the deposition of microthrombi, diffuse capillary obstruction, and the resultant ischemia subsequently causing organ damage. The tissue damage that arises as a sequel to the above processes leads to further inflammation, and hence a vicious cycle ensues with additional inflammation leading to further coagulopathy, tissue damage, and increased risk of morbidity and mortality.[27, 28] Current evidence demonstrates that >71% of patients who died from COVID-19 met the International Society on Thrombosis and Hemostasis (ISTH) criteria for DIC.[29] These patients' coagulation profile were typically characterized by higher serum D-dimers, lower antithrombin III levels and higher fibrin degradation products compared to healthy controls.[30]

Clinical Features

Since the emergence of the pandemic, there have been a multitude of clinical series published regarding the clinical manifestations and outcomes of COVID-19.[12, 31-34] Majority of the initial symptoms were related to the upper respiratory tract and gastrointestinal system, and varied significantly in severity between affected subjects. The common initial symptoms included; cough, dyspnea, fatigue, and myalgia. [35]Additional minor symptoms included; headaches, and diarrhea.[36]

The median incubation period has been reported to be five (5) days and individuals who develop symptoms do so within approximately eleven and a half (11.5) days of infection.[37] The

median time from onset of initial symptoms to dyspnea is eight (8) days.[38] [39] In some cases, the disease rapidly progressed to acute respiratory distress syndrome and septic shock, while in others, the disease took a milder course.[39] Critically-ill patients who required mechanical ventilation (15/21; 71%) typically presented with major multi-organ complications.[31, 32, 40] These included non-atherosclerotic ST-elevation myocardial infarction, interstitial pulmonary tissue edema, acute kidney failure (ARF), brainstem infarcts, liver dysfunction, skin petechial rashes, and gastrointestinal mucosal bleeding. Patients with such complications often experienced worse outcomes. For example, patients with reported cardiac injury and/or dysfunction were observed to have significantly higher morbidity and mortality. ($P < .001$).[31] COVID-19 has been reported to be complicated by neurological dysfunction and stroke.[14, 41] There are various studies that have reported neurologic dysfunction and acute stroke as presenting symptoms in COVID-19 patients.[42] [14, 41, 43] The hypercoagulable state is likely due to sepsis induced coagulopathy, a known precursor to Disseminated Intravascular Coagulation (DIC).[41] One Dutch Study reported on outcomes of 184 ICU patients with confirmed COVID-19 and found a 31% incidence of thrombotic complications including ischemic stroke.[14] In another study, 78/214 (36.4%) patients had neurological manifestations and severe infection was associated with neurologic manifestations such as impaired consciousness (13 [14.8%] vs 3 [2.4%]), acute cerebrovascular disease (5 [5.7%] vs 1 [0.8%]) and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]).[43]

Organ System Complications

Cardiac

In addition to the known initial pulmonary consequences of COVID-19, various reports have demonstrated that patients infected with SARS-CoV2 can develop cardiac dysfunction and myocardial injury.[44, 45] The mechanism of myocardial injury is unclear, but several have been proposed that severe respiratory dysfunction and consequential hypoxemia leads to increased myocardial demand, mixed severe respiratory and metabolic acidosis, which then results in myocardial injury and cellular apoptosis.[12] Others propose that severe cytokine storm resulting from the host hyper-immune response to the primary SARS-CoV2 infection leads to secondary myocarditis, acute heart failure, malignant arrhythmias, and demand ischemia (**Figure 2 & 3**).[46, 47] In addition, emerging reports suggest that SARS-CoV2 may act directly on myocardial tissue since ACE2 is presumed to be expressed on the myocardium with adequate quantities.[44, 48] Primary viral myocarditis can occur with viruses such as cytomegalovirus (CMV) and Rubella but has not yet been confirmed with SARS-CoV infections.[49-51] The occurrence of primary COVID-19 induced myocarditis would be a novel finding and may be consistent with recently reported echocardiographic findings that resemble other primary infectious myocardial complications such as Kawasaki syndrome.[52, 53]

Reports have demonstrated that acute cardiac injury incidence ranges between 7 to 17% among hospitalized patients.[33, 35, 38] In a single-center case series, involving 138 patients, patients who were critically ill with COVID-infection were more likely to have elevated myocardial injury serum biomarkers (Troponin I and CK-MB).[35] In a separate single center observational study involving 120 patients admitted to the hospital for symptoms associated with COVID-19, 27.5% and 10% of the patients were found to have elevated levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) and Troponin I, respectively.[11] In another retrospective single center case series of 187 patients with COVID-19, the authors observed that 27.8% of patients

had myocardial injury that resulted in cardiac dysfunction and arrhythmias. Notably, patients with elevated troponins had 6.7 times higher odds of mortality compared to those with normal troponin levels. [54] In this study and others, patients with cardiovascular risk factors such as coronary heart disease, hypertension and cardiomyopathy were at higher risk of mortality.[44, 54] Non-occlusive STEMI in presumed to be the cause of cardiac enzyme release, which suggests that primary cardiac pathology in the setting of COVID-19 may not necessarily be associated with underlying arterial thromboembolic occlusive disease.[55, 56]

Arrhythmias have also been observed as another common cardiac manifestation in patients with COVID-19. However, the type of arrhythmias have not yet been clearly characterized. One study suggested the most common abnormal rhythm observed was sinus tachycardia, which was present in >71% of the 121 patients diagnosed with COVID-19.[52] Bradycardia was observed in >14% of patients, and one patient was reported to have transient atrial fibrillation. [52] It is unclear whether the arrhythmias are primarily a complication of COVID-19, adverse effect of medication administered, or whether they are a result of exacerbation of the previously underlying heart disease. Some reports have cited malignant tachyarrhythmias as a strong predictor of mortality.[11, 12, 35, 57] In a study by Guo et al,[54] patients with elevated troponin levels were observed to develop malignant ventricular arrhythmias compared to those with normal troponins (11.5% vs 5.2%). In a retrospective study involving 191 patients, heart failure was observed in 23% of patients with COVID-19 and was associated with an elevated risk of mortality (up to 28%).[33] It is unclear if heart failure is an exacerbation of pre-existing heart disease or if it is due to myocarditis or stress cardiomyopathy.[58]

Various treatment modalities have been employed in the treatment of patients with COVID-19 and cardiac manifestations. In one study patients with elevated cardiac enzymes were

also more likely to receive glucocorticoid therapy and receive mechanical ventilation compared to patients with normal cardiac enzymes (71.2% vs 51.1%) and (59.6% vs 10.4%) respectively.[54] A case report of a 37 year old woman who was diagnosed with fulminant myocarditis, cardiogenic shock, and severe pulmonary infection related to COVID-19, was managed with methylprednisolone, immunoglobulins, milrinone, and diuresis.[45] The authors reported that after a 3 weeks treatment course the patient's myocardial injury biomarkers biomarkers had normalized.[45] Antivirals such as ribavirin, redmesvir, and oseltamivir, and antibiotics such as ceftriaxone, azithromycin, and immunoglobulins to modulate the immune status have also been reported with variable success.[11, 52, 57] In addition, there have been reports on the utilization of invasive and non-invasive ventilation, extracorporeal membrane oxygenation, and intra-aortic balloon pump as rescue therapy manuvers.[35] [11, 12, 45]

Renal

Initial reports from Wuhan, China informed us that acute kidney injury (AKI) occurred in 7% of individuals who are COVID-19 positive.[38] In patients who developed severe infection and required hospitalization, kidney abnormalities were observed in 25-50% of patients, and manifestations included acute proteinuria and hematuria.[59] In a prospective cohort of 701 patients, from 3 different hospital centers in China, the authors observed that 43.9% of patients had proteinuria and 26.7% had hematuria, and were reported as adjusted risk factors for in-hospital death.[60]

The ACE2 receptor is known to be expressed in the renal capillary,[17] and is thought to lead to localized tissue inflammation due to COVID-19 infections. In one case series, a 71 year old renal transplant recipient infected by COVID-19 demonstrated viral inclusion structures in the endothelium on electron microscopy, and inflammatory cells associated with endothelium

were visualized on tissue histology. Another patient in this series demonstrated evidence of post mortem endothelitis in various organs including the kidneys. Finally, in another study that evaluated postmortem renal histopathological in 26 patients observed diffuse proximal tubule injury, red blood cell aggregates obstructing capillary lumens, and clusters of coronavirus particles in the tubular epithelium.[61]

Several mechanisms of COVID-19 induced renal injury have been proposed. One potential mechanism may simply be due to hypo-perfusion from dehydration and diarrhea related to the systemic inflammatory.[62-64] However, this mechanism would not necessarily explain findings of proteinuria and hematuria, which are not typically observed with other pre-renal conditions.[64] An alterative hypothesis is that COVID-19 induced endothelial dysfunction may be disruptive to the vascular hemostatic equilibrium that shifts it towards a more vasoconstrictive state. This microangiopathic effect can lead to acute tissue malperfusion, ischemia, and a pro-coagulation state.[65, 66]

The care of patients impacted by COVID-19 related AKI remains largely supportive. Depending on the severity of the presentation, patients may be managed with renal replacement therapy (RRT) in the form of intermittent hemodialysis or continuous renal replacement therapy (CRRT), or slow low efficiency dialysis (SLED). In the current absence of data clearly demonstrating superiority of one modality over another, the choice of dialysis modality is mostly informed by the availability of resources and local clinical expertise.[63]

Venous thromboembolism (VTE)

Coagulopathy is a common phenomenon that can occur with sepsis and may predict outcomes in patients with severe pulmonary infections and multisystem organ dysfunction.[67]

Several reports indicate that patients with COVID-19 infections who are critically-ill are at increased risk of developing VTE, including deep venous thrombosis (DVT) and pulmonary emboli (PE).[68-70] In a single center cohort study of 198 patients, 20% of patients were diagnosed with VTE and with extensive symptomatic thrombophlebitis for which anticoagulation treatment was initiated.[71] The cumulative incidences of VTE at 7, 14, and 21 days was found to be 16% 33%, and 42% respectively.[71] The authors also reported that VTE was significantly associated with death, with a hazard ratio of 2.7. In a separate single center study of 147 patients admitted to hospital for COVID-19, 17% were found to have VTE.[72] Of these patients, 64% had acute PE, and 56% had acute DVT, and the all cause mortality in these patients was significantly greater when compared to patients with no VTE (48% vs 22%) (**Figure 4**).[72]

Some screening serum biomarkers have been proposed to monitor severity and incidence of VTE. In one study an admission D-dimer level >1,500ng/mL was found to be an independent marker associated with the incidence of VTE.[72] In another retrospective single center study with a total of 81 patients diagnosed with severe COVID-19 pneumonia admitted to the intensive care unit (ICU), D-dimer level >1,500ng/mL again was a good index for identifying high risk groups.[73] Similarly, in another study of 150 patients who were admitted to ICU due to COVID-19 infections, serum Von Willebrand (vWF) activity, vWF antigen, and FVIII were considerably increased, and 87.7% had positive lupus anticoagulant.[74]

Multiple studies have demonstrated overall higher index of morbidity and mortality in patients affected by VTE.[75-77] For example, in a Dutch cohort of 184 patients who were admitted to ICU with COVID-19, the authors observed an adjusted cumulative incidence of symptomatic acute PE, DVT, ischemic stroke, myocardial infarction and /or systemic arterial embolism of 49%, and that the majority of the thrombotic events were Pulmonary embolism (65/75; 87%). [77]

Patients with thrombotic complications were at a higher risk of all-cause mortality (HR 5.4) and the use of therapeutic anticoagulation was associated with a 21% increased likelihood of survival (all-cause mortality HR 0.79).[77]

Treatment Strategies

The treatment of COVID-19 associated microvascular angiopathies and their affects on the cardiovascular system is yet to be defined, but various strategies can potentially be derived from treatments used for management of other microvascular angiopathies. Conditions such as Kawasaki's disease, Henoch-Schonlein purpura, Rheumatoid Arthritis and Buerger's disease, are typically managed by targeting the underlying disorder and palliating symptoms.[78, 79 80-82] Some are vasculitidies responsive to treatment with immunoglobulins, calcium channel blockers, thrombolytics, prostaglandin analogues, glucocorticoids, and other immune-modulators such as methotrexate.[78, 80, 82] Various such agents have been used in the battle against COVID-19 with variable success.[12, 29, 70, 83-88]

Anti-Virals

On May 1st, 2020 the Food and drug administration (FDA) issued an emergency use authorization of Remdesivir for adults and children with suspected or laboratory confirmed severe COVID-19.[83] Remdesivir binds and inhibits the RNA-dependent RNA polymerase that is essential for SARS-CoV2 viral replication.[85] In a study of 61 patients with confirmed severe COVID-19 and evidence of hypoxia (56% receiving mechanical ventilation and 8% receiving veno-venous or veno-arterial extracorporeal bypass), at least one dose of remdesivir on a compassionate use basis, demonstrated clinical improvement and improved heart function in

68% of patients.[89] Similarly, in a randomized double-blind placebo-controlled multicenter trial, comprising of 237 patients, the authors reported that remdesivir was not associated with statistically significant clinical benefits, however the numerically faster time to clinical improvement requires confirmation in larger studies.[90] Other antivirals like lopinavir and ritonavir (used for treatment of HIV), ribavirin (used for treatment of Hepatitis C), are under clinical investigation for the treatment of COVID-19.[83, 86, 91]

Anti-Coagulation

Anticoagulants have recently emerged as an important treatment modality for patients infected with COVID-19, and in particular patients who are considered higher risk individuals.[92] Various institutional guidelines have recommended initiation of prophylactic or therapeutic anticoagulation in patients impacted by COVID-19.[93 94-96] In one retrospective study, it was observed that patients who received either prophylactic or therapeutic anticoagulation had lower incidence of myocardial dysfunction, mechanical ventilation, and in-hospital mortality.[95] In another study, of 2,773 COVID-19 positive patients who were receiving mechanical ventilation, the hospital mortality rate was significantly reduced in patients that received therapeutic anticoagulation (62.7% vs 29.1%).[97] Despite these clear advantages in the application of therapeutic anticoagulation in patients afflicted with COVID-19 and who are critically-ill, there remains important unanswered questions about the role, duration of therapy, and potential consequences of anticoagulation therapy. It is also unclear whether anticoagulation therapy may be used to help in prophylaxis against COVID-19 induced multi-organ dysfunction.

Steroids

Steroid therapy has been used for the treatment of severe acute respiratory distress syndrome (ARDS) due to COVID-19 infection.[12] In a multi-center study of 213 patients with moderate to severe COVID-19 related symptoms, it was found that patient who were treated with methylprednisolone had a reduced incidence of escalation of care and improved clinical and cardiac outcomes.[98] Similarly, in a multicenter partially randomized, preference open label trial, patients with a COVID-19 pneumonia, impaired gas exchange, and biochemical evidence of hyper-inflammation, demonstrated reduced incidence of death, cardiac dysfunction, ICU admission, and non-invasive ventilation following treatment with methylprednisolone.[99] In another multicenter observational study, methylprednisolone administration in patients with severe COVID-19 pneumonia significantly lowered rates of ventilator dependence, myocardial infarction, and death.[100]

Conclusion

The body of evidence demonstrating the role of microvascular angiopathy in COVID-19 is building rapidly. We have stated and summarized some of these findings here. However, more research into the molecular, biochemical and pathophysiological mechanisms underlying this new disease amidst us is of paramount importance as this not only helps in vaccine development processes but also in inventing a possible cure.

Figure legends

Figure 1. Schematic summary of the COVID-19 microangiopathic consequences leading to myocarditis, non-occlusive STEMI, arrhythmia, heart failure, vascular thrombosis, and microvascular renal dysfunction.

Figure 2. Intraoperative trans-esophageal echocardiography (TEE) in a COVID-19 positive patient with myocarditis, acute pericardial effusion and cardiac tamponade. After bedside venous-arterial extracorporeal membrane oxygenation (VA-ECMO) cannulation was performed, the patient was taken to the operating room emergently for ventral cardiac window exposure and decompression of the pericardial effusion. (A) Preoperative mid-esophageal four chamber view demonstrated severely reduced global left ventricle (LV) function. (B & C) Similarly, mid-esophageal long axis view demonstrated severely reduced LV contraction. (D) Transgastric short axis view demonstrated under-filling of the LV. Patient was taken emergently to the operating room for cardiac window decompression of the pericardial effusion and a large pericardial effusion. An Impella device is seen in the LV.

Figure 3. Transthoracic echocardiography (TTE) in a COVID-19 positive patient who presented with acute bilateral pulmonary emboli and acute right sided heart failure requiring emergent veno-venous extracorporeal membrane oxygenation (VV-ECMO) cannulation. (A) Parasternal long axis view demonstrate a McConnell's sign: Right ventricle (RV) enlargement and hypokinesis with preserved apical contractility. (B) Optison enhanced images demonstrate RV enlargement, and paradoxical septal motion consistent with RV dysfunction.

Figure 4. Computed tomographic (CT) images of a COVID-19 positive patient who presented with bilateral lobar pulmonary embolism (white arrows; A-D), and right ventricular enlargement and bowing of the interventricular septum to the left, consistent with right heart strain (red line; E).

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