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CONTEMPORARY REVIEW

Coronavirus Disease 2019 and the Cerebrovascular-Cardiovascular Systems: What Do We Know So Far?

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ABSTRACT: The severe acute respiratory syndrome coronavirus 2 pandemic of 2019 to 2020 has resulted in multiple hospitalizations, deaths, and economic hardships worldwide. Although respiratory involvement in patients with coronavirus disease 2019 (COVID-19) is well known, the potential cardiovascular and cerebrovascular manifestations are less understood. We performed a PubMed and Google Scholar search and reviewed relevant literature on COVID-19 and cardiovascular system involvement. Severe acute respiratory syndrome coronavirus 2 possesses high affinity for angiotensin-converting enzyme 2 receptor, which is highly concentrated in the lungs and cardiovascular tissue, thereby provoking concern for cardiovascular involvement in COVID-19 cases. Preexisting cardiovascular and cerebrovascular disease has been shown in previous reports to be a risk factor for severe infection. On the basis of our review of published studies, COVID-19 patients may be more likely to experience acute cardiac injury, arrhythmia, coagulation defects, and acute stroke and are likely to have poorer outcomes as a result. As the COVID-19 pandemic continues, more data about potential cardiovascular and cerebrovascular manifestations of the disease are required.

Key Words: cardiac disease ■ cerebrovascular disease/stroke ■ COVID-19 ■ coronavirus ■ SARS-CoV-2 ■ vascular disease

A novel coronavirus with an alarmingly high transmissibility has resulted in an ongoing pandemic.[1] In infected individuals, this unique coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), results in coronavirus disease 2019 (COVID-19).[2] SARS-CoV-2 has a higher capacity for transmission compared with the SARS coronavirus that caused an outbreak in 2003. It is well understood that SARS-CoV-2 most commonly causes a viral pneumonia, resulting in alveolar damage and progressive respiratory distress.[3–5] The cardiovascular implications of SARS-CoV-2, however, remain poorly recognized. Early reports have indicated that patients with COVID-19 may have cardiovascular manifestations and that preexisting cardiovascular morbidities may result in poorer outcomes.[6] An understanding of potential cardiovascular and cerebrovascular manifestations in COVID-19 cases is crucial to appropriately care for afflicted patients. We review the published literature to summarize the cumulative findings of cerebrovascular-cardiovascular diseases related to COVID-19 in addition to discussing potential pathophysiological mechanisms.

METHODS

The authors declare that all supporting data are available within the article. We performed a PubMed and Google Scholar literature search on March 23, 2020. Key search terms used included “COVID-19,” “coronavirus,” “SARS-CoV-2,” “vascular,” “cardiovascular,” “cerebrovascular,” “stroke,” “vessel,” “cardiac,” “heart,” and “ACE2.” Relevant articles were reviewed in full, and the reference lists were scrutinized for any additional relevant sources. There were no strict inclusion or exclusion criteria. No statistical analyses were performed.

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin receptor blocker
COVID-19	coronavirus disease 2019
ICU	intensive care unit
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SARS-COV-2: BACKGROUND

SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus that belongs to the coronaviridae family of viruses.[7] Coronavirus genomes code for an array of proteins that can be classified into 2 primary categories: structural and nonstructural.[7] Nonstructural proteins largely function in replication processes, whereas structural proteins are crucial for virion assembly, host-cell binding, tissue tropism, and infection.[7,8] S proteins, otherwise known as "spike" proteins, are located on the viral surface and are responsible for initial attachment of the virion to the host cell receptor and are therefore the major determinant of the host species and tissue tropism of the virus.[8,9] Following S protein binding, proteolytic cleavage of S protein subunits results in fusion of the viral and host cell membranes with subsequent release of the viral genome into the host-cell cytosol. Replication and transcription of viral RNA within the host cell ensues, thereby producing the necessary components for progeny virion assembly and release.[7,8]

Angiotensin-converting enzyme 2 (ACE2) is a transmembrane metalloprotease that is found in multiple tissues, including heart, lung, and kidney, and plays a crucial role in cardiovascular physiological characteristics.[10,11] In 2003, ACE2 was identified as a novel host cell surface receptor for SARS coronavirus S protein,[11,12] and SARS-CoV-2 has also been shown to have high binding affinity for ACE2.[13,14] In tissues with sufficient levels of ACE2 expression, binding of SARS-CoV-2 S protein leads to infection. Single-cell RNA expression studies have shown that type 2 alveolar cells express relatively high levels of ACE2,[15] likely explaining the high prevalence of severe respiratory symptoms among COVID-19 cases. As an important regulator of hemodynamic homeostasis, ACE2 is expressed in vascular cells, such as vascular smooth muscle cells and endothelial cells of the arterial and venous systems of most organs.[16,17] Given the high affinity of SARS-CoV-2 for ACE2, these critical cardiovascular tissues may be at risk for infection.

CARDIAC INVOLVEMENT

To date, cardiac involvement of SARS-CoV-2 has not been directly investigated; nevertheless, cardiac manifestations in COVID-19 require consideration. Several reports provide evidence that patients with preexisting cardiovascular comorbidities, including hypertension, diabetes mellitus, and coronary artery disease, were more likely to have severe disease and require intensive care unit (ICU) care.[4,5,18–21] Cases of acute cardiac injury in COVID-19 patients continue to mount, primarily from several Chinese cohort studies that have reported elevated cardiac troponin levels among infected patients.[6,20,22] In fact, cases of COVID-19 with elevated troponin levels have been shown to be more likely to necessitate ICU-level care, or result in death.[6,20] The prevalence of acute cardiac injury has been reported to be ≈7% of all patients and as high as 31% of all ICU patients diagnosed with laboratory-confirmed COVID-19 by some early studies.[4,6] Lippi et al[23] performed a meta-analysis that included a total of 341 patients from 4 Chinese studies and found that the standardized mean of cardiac troponin levels was significantly higher in those with severe COVID-19–related illness compared with those with nonsevere disease, further implicating the potential for cardiac injury from COVID-19 and the resulting poor prognosis that may result. Other adverse cardiac events, including arrythmias and worsening heart failure, have been reported in the context of COVID-19.[4,19,24]

Cases of fulminant viral myocarditis have also been described in 2 separate reports.[25,26] In both instances, intravenous immunoglobulin and glucocorticoids were used for treatment, and both patients had recovery in cardiac function within weeks. The efficacy of these 2 therapeutics in cases of myocarditis in the setting of COVID-19, however, remains largely untested and uncertain. Although the true prevalence of myocarditis among COVID-19 patients remains unknown, these select reports indicate it is likely low. Despite limited data, early reports describe a concerning potential for COVID-19 cases to manifest with cardiac-related complications, therefore requiring careful consideration among these patients. More intensive care for patients with preexisting cardiovascular disease may be implicated.

Many patients with hypertension and diabetes mellitus are treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Administration of these drugs to patients with diabetes mellitus and hypertension has been shown to cause upregulation of ACE2 receptor levels.[27,28] Given the tropism of SARS-CoV-2 for the ACE2 receptor, concern exists that patients treated with ACEi or ARBs may be at increased risk for severe

infection. A recent study of hypertensive COVID-19 patients hospitalized in Wuhan, China, found no difference in the percentage of patients taking ACEi/ARBs between those with severe infection and those with nonsevere infection.[29] There was also no difference when comparing survivors and nonsurvivors, and this finding remained true when data were analyzed separately for patients taking ARBs and those taking ACEi. These early results suggest that patients currently taking ACEi and ARBs for management of hypertension are not at increased risk for severe infection or death from SARS-CoV-2. This finding supports prior recommendations from major governing bodies in the United States and Europe, which state that patients should not cease ARB/ACEi therapy out of concern for COVID-19.[30,31]

The mechanisms by which SARS-CoV-2 results in cardiac injury are poorly understood, although several plausible theories may be considered. Human cardiac tissue possesses a relatively high expression level of ACE2.[17,32] SARS-CoV-2 may therefore directly infect myocardial tissue, particularly in cases of advanced viremia. Prior studies have shown that SARS coronavirus pulmonary infection provokes an ACE2-dependent myocardial infection in a mouse model.[33] Such an infection may result in a localized inflammatory response with subsequent myocarditis leading to acute cardiac injury and the potential for arrythmias or heart failure.[34] In addition to case reports, postmortem findings in COVID-19 patients have demonstrated the presence of a mononuclear inflammatory myocardial infiltrate potentially supporting this hypothesis.[3] ACE2 plays a crucial role in cardiovascular homeostasis. For example, ACE2-deficient mice have been shown to have reduced cardiac contractility, reduced ventricular pressure, and decreases in arterial pressure.[35] Viral disruption of this signaling pathway may result in disturbances in cardiac function and other hemodynamic parameters.[34] Patients with preexisting cardiomyopathy have upregulated ACE2 levels at baseline, potentially placing them at higher risk for cardiac detriments in cases of COVID-19. Increasingly, immunological derangements are being recognized in COVID-19 patients. Given that dysregulated immunological status has been correlated with an increased risk of cardiovascular disease,[36,37] an indirect mechanism of immunological dysfunction leading to cardiac sequelae may also be at play.[34] A large majority of COVID-19 cases manifest as respiratory distress with resultant hypoxemia, which may therefore incur cardiac injury secondary to an oxygen supply and demand mismatch. The potential mechanisms of cerebrovascular-cardiovascular involvement in cases of COVID-19 are illustrated in the Figure. These potential explanations of cardiac pathomechanics in context of COVID-19 are highly speculative in nature, and the underpinnings of cardiac involvement are complex and likely multifactorial, thereby warranting further investigation.

COAGULATION ABNORMALITIES

To date, data about coagulation abnormalities in COVID-19 cases remain limited, although several early Chinese reports have implicated coagulation disturbances in infected patients, thereby prompting consideration. Elevations in D-dimer levels have been more

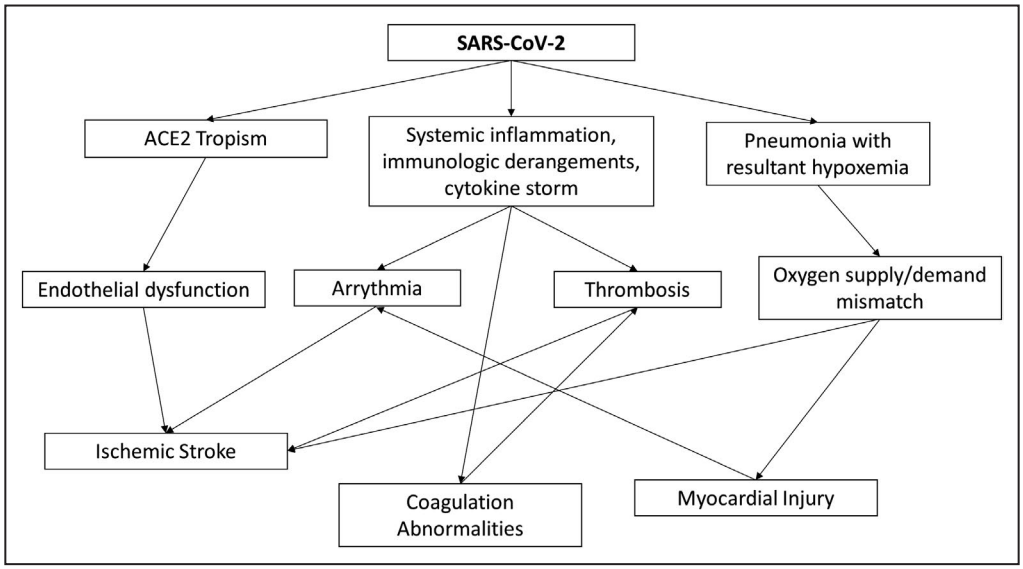

Figure. Diagrammatic representation of potential mechanisms of cerebrovascular-cardiovascular manifestations in cases of coronavirus disease 2019.
ACE2 indicates angiotensin-converting enzyme 2; and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

prevalent in patients with severe disease,[6,18] and have even shown a higher prevalence in COVID-19 patients who have eventually died.[38] Similar patterns were also observed with elevated fibrin degradation products, prothrombin time, and activated partial thromboplastin time.[38] A multicenter retrospective cohort study performed by Zhou and colleagues[24] found elevated D-dimer levels to be strongly associated with in-hospital death (odds ratio, 18.4; 95% CI, 2.6–128.6; *P*=0.003). A high prevalence of thrombotic complications has also been evident in other geographical regions as well, with up to 31% of ICU patients being affected in some European reports.[39,40] As another potential coagulation-based complication, viral infiltration of vascular tissue via ACE2 may result in endothelial dysfunction with the potential for thromboembolic complications.[34] Activation of the complement system has also been suggested to play a role in the high rates of thrombotic complications of COVID-19 patients.[41] In addition, hypercoagulability resulting from antiphospholipid antibody syndrome has been described, although this potential association is uncertain.[42] A more advanced understanding of how COVID-19 results in various disturbances in coagulation is needed. Regardless, these prior reports suggest the importance of considering the potential coagulation defects in COVID-19 cases. Clinicians may therefore be more apt to consider prophylactic measures in hospitalized COVID-19 patients.

CEREBROVASCULAR MANIFESTATIONS

Early reports demonstrate that cerebrovascular disease seems to play an important role in infected individuals. Chen et al,[5] of Wuhan, China, found that 40% of admitted patients had concomitant cerebrovascular and cardiovascular disease. Guan et al[18] found that in 67 patients who reached the primary composite end point in their study (defined as ICU admission, mechanical ventilation, or death), 4 (6%) had preexisting cerebrovascular disease, compared with 11 of 1032 (1.1%) who did not reach the primary composite end point. In a study of 138 hospitalized COVID-19 patients in Wuhan, Wang et al[4] documented 7 patients (5.1%) had comorbid cerebrovascular disease. Of 36 ICU admissions, 6 patients had comorbid cerebrovascular disease (16.7%), compared with 1 of 102 patients not requiring ICU admission (1.0%) (*P*=0.001). In a single-center retrospective study of 221 admitted COVID-19 patients in Wuhan, Li et al[43] found that 13 patients (5.9%) developed acute cerebrovascular events. Of these patients, 11 had acute ischemic stroke (5% of admitted COVID-19 patients), 1 (0.5%) had cerebral venous sinus thrombosis, and 1 (0.5%) had intracerebral hemorrhage. Patients with concomitant cerebrovascular disease were more likely to be older, were more likely to have preexisting cardiovascular comorbidities, and were more likely to have severe infection. Other studies from Wuhan have also reported similar prevalences of acute cerebrovascular events in association with severe infection.[44] These early reports suggest that, first, concomitant cerebrovascular disease may result in a worse prognosis in COVID-19 patients, and second, acute cerebrovascular events, including ischemic stroke, are not uncommon among infected patients.

As the COVID-19 pandemic continues to progress, cerebrovascular manifestations of COVID-19 may become more evident. Earlier reports of acute ischemic stroke in patients with Middle East respiratory syndrome coronavirus and SARS coronavirus

Table. Summary of Cerebrovascular-Cardiovascular Manifestations in the Context of COVID-19 on the Basis of Prior Studies[4-6,18,23,25,26,29,38-40,43]

System	Main Points
Cardiac	• Up to 40% of infected patients have comorbid cardiovascular or cerebrovascular disease. • Patients with preexisting cardiovascular comorbidities, including hypertension, diabetes mellitus, and coronary artery disease, are more likely to require ICU admission, require mechanical ventilation, or die. • Elevated troponin levels have been found in 7% to 12% of all patients, and from 22% to 31% of ICU-level patients diagnosed with COVID-19. • Acute cardiac injury in the setting of COVID-19 is associated with worse outcomes. • Viral myocarditis appears to be rare, with few reported cases to date. • Early reports suggest patients taking ACEi/ARBs are not at increased risk for severe infection.
Coagulation	• Abnormal coagulation laboratory results in COVID-19 patients have been commonly observed. • A high prevalence of thrombotic complications has been reported, up to 31% by some reports. • Up to 69% of patients requiring mechanical ventilation, those requiring ICU admission, or who died had elevated D-dimer levels.
Cerebrovascular	• Patients with preexisting cerebrovascular disease are more likely to have worse outcomes. • Acute cerebrovascular events, including ischemic stroke, have been reported in up to 5.9% of hospitalized COVID-19 patients, as reported in some early studies. • Patients with severe infection are more likely to develop acute cerebrovascular disease than those with less severe infection.

ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; and ICU, intensive care unit.

have been documented, although these reports are anecdotal and limited by multiple confounding factors.[45,46] Nevertheless, COVID-19 patients may be at risk for cerebrovascular manifestations for multiple reasons. First, ACE2 has been found to be expressed within venous and arterial tissue within the brain,[17] and considering the high affinity of SARS-CoV-2 for this receptor, it is plausible that viral infection of vascular tissue of the brain may occur. However, such occurrences have yet to be specifically demonstrated with histopathological studies. Second, COVID-19 cases with concurrent cardiac arrhythmia may increase the likelihood of cardioembolism formation,[4] and therefore preventative measures in these patients may be implicated. In the report by Li et al,[43] 3 of the 11 (27.3%) acute ischemic strokes were thought to be of cardioembolic nature. Third, coagulation defects found to be prevalent in severe cases of COVID-19 may predispose to thromboembolic events within the brain. Interestingly, Li et al[43] found that patients with cerebrovascular manifestations with COVID-19 had significantly higher average D-dimer and CRP (C-reactive protein) levels, potentially suggesting an inflammatory-induced hypercoagulable state resulting in stroke. Finally, patients with preexisting cerebrovascular disease, resulting in intracranial stenosis with hypoperfused brain regions, may be at increased risk for ischemic stroke while in a state of severe infection and systemic inflammation. In the Li et al study,[43] 5 of 11 patients (45.5%) with acute stroke were found to have large-vessel stenosis, potentially supporting this hypothesis. The mechanism of cerebrovascular manifestation in COVID-19 patients is complex and likely multifactorial. Regardless, the putative risk for cerebrovascular manifestations in COVID-19 cases requires consideration from caregivers. Reports of management strategies in COVID-19 patients with acute cerebrovascular events are absent from the literature at this point. Reporting of such cases is therefore crucial to better estimate risk and establish appropriate care guidelines.

CONCLUSIONS

A summary of the main points of this review can be found in the Table. The COVID-19 pandemic represents a worldwide health emergency as novel cases and mortality continue to climb in multiple areas. Although the severe respiratory manifestations incurred by the SARS-CoV-2 virus are well known, involvement of the cardiovascular and cerebrovascular systems requires consideration. As the pandemic continues, accurate and thorough scientific reporting remains crucial to further our understanding of the potential vascular manifestations in COVID-19 cases.

ARTICLE INFORMATION

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