Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW

COVID-19 and Microvascular Disease: Pathophysiology of SARS-CoV-2 Infection With Focus on the Renin-Angiotensin System

Daniel Arthur Kasal, MD, PhD [a,b,*], **Andrea De Lorenzo, MD, PhD** [a], **Eduardo Tibiriçá, MD, PhD** [a]

[a]National Institute of Cardiology, Ministry of Health, Rio de Janeiro, Brazil
[b]State University of Rio de Janeiro, Internal Medicine Department, Rio de Janeiro, Brazil

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The recently described severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people, with thousands of fatalities. It has prompted global efforts in research, with focus on the pathophysiology of coronavirus disease-19 (COVID-19), and a rapid surge of publications. COVID-19 has been associated with a myriad of clinical manifestations, including the lungs, heart, kidneys, central nervous system, gastrointestinal system, skin, and blood coagulation abnormalities. The endothelium plays a key role in organ dysfunction associated with severe infection, and current data suggest that it is also involved in SARS-CoV-2-induced sepsis. This critical review aimed to address a possible unifying mechanism underlying the diverse complications of COVID-19: microvascular dysfunction, with emphasis on the renin-angiotensin system. In addition, research perspectives are suggested in order to expand understanding of the pathophysiology of the infection.

Keywords COVID-19 • Microcirculation • Renin-angiotensin system

Introduction

Seven (7) months after the first case descriptions of the coronavirus disease 19 (COVID-19) and the identification of the causal agent [1], the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been diagnosed in almost 15,000,000 people and claimed >617,000 lives (accessed 22 July 2020 https://coronavirus.jhu.edu/map.html). Global efforts in research, including the pathophysiology of COVID-19, have been undertaken, with a rapid and rarely seen surge of publications related to a single disease, within months [2]. Accordingly, COVID-19 has been associated with a myriad of clinical manifestations, including the lungs [3], heart [4], kidneys [5], central nervous system [6], gastrointestinal system [7], skin [8], and blood coagulation abnormalities [9].

During infection, the endothelium displays an essential role in the physiological adaptive processes, adjusting blood flow to regions of increased metabolic demand and enabling the access of immune defence cells to the site of infection [10]. When activated by sepsis, dysfunctional endothelium can lead to intravascular thrombosis, amplification of the inflammatory process and disturbances in regional blood flow [11]. As a consequence, endothelial dysfunction is considered the main factor leading to organ failure in sepsis [12]. Understanding the molecular pathways involved in vascular pathophysiology during sepsis is a key step towards the development of therapy strategies.

The renin-angiotensin system (RAS) is essential for vascular homeostasis, with actions ranging from plasma volume regulation to vascular tone and inflammation [13,14]. In severe bacterial sepsis, previous studies have

*Corresponding author at: Rua das Laranjeiras 374, 22240-006, Rio de Janeiro, Brazil. Tel.: +55-21-3037-2141; Email: dabkasal@gmail.com

demonstrated RAS activation [15,16]. Severe COVID-19 has been viewed as viral sepsis, followed by exuberant cytokine production [17], and also associated with RAS imbalance.

The present review aimed to address microvascular dysfunction as a possible unifying mechanism underlying the diverse manifestations of COVID-19, with emphasis on the interactions with RAS.

COVID-19 as a Microvascular Disease

Microcirculation is well recognised as a component of the response to pathogens, which can be either adaptive or dysfunctional. The physiological microvascular response that occurs in mild to moderate infection characterises most of the classical signs of inflammation (Latin, *calor, dolor, rubor, tumor*) and is a direct result of cytokine-driven vasodilation at the site of pathogen inoculation [18]. Contrary to this are the extensive abnormalities of endothelial function, which may occur in sepsis, associated with disseminated intravascular coagulation (DIC) [19] and a heterogeneous vasomotor response, where hypotension and shock are associated with microvascular vasoconstriction [20]. Previous evidence of microvascular dysfunction associated with acute viral infection was provided during the influenza A (H1N1) pandemic. Salgado et al. evaluated microcirculation in critical patients with acute lung injury [21]. The degree of microvascular dysfunction correlated with the severity of the disease, as measured by the Sequential Organ Failure Assessment (SOFA) score.

The effects of inflammation on endothelial cells include increased expression of adhesion molecules, stimulated by proinflammatory cytokines and chemokines such as IL-1β and TNF-α, and C-reactive protein, that is produced in response to IL-6, amongst others [22,23]. Thrombotic phenomena, reflecting a close relationship between increased proinflammatory cytokines, may ensue endothelial dysfunction and vascular thrombosis. Patients with severe COVID-19 have displayed the 'cytokine storm' [24], in which proinflammatory cytokines are increased, culminating in multiorgan injury. This has been hypothesised as an exaggerated host immune system response, similar to the findings of other severe viral pneumonias such as influenza, avian influenza, and severe acute respiratory syndrome [25,26]. The vicious cycle involving cytokine overproduction and microvascular endothelial injury appears to be an essential factor leading patients with severe COVID-19 to multiple organ failure and even death [27,28]. Thus, therapeutic interventions to mitigate inflammatory organ injury have been proposed, and the beneficial role of corticosteroids for patients with COVID-19 who required respiratory support has recently been shown in the Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial [29]. Interestingly, another effect of corticosteroids, via mineralocorticoid receptor binding, has also been suggested in COVID-19, with possible interplay with RAS [30].

Most current studies of COVID-19 are focussed on the macrocirculation, evaluating systemic arterial pressure, the use of vasopressors, and systemic markers of impaired tissue perfusion such as lactate. As a consequence, the reported prevalence of septic shock in adults with a diagnosis of COVID-19 ranges between 20–35%, according to the population studied, the severity of the patient sample and the definition of septic shock that is used [31,32].

Notwithstanding, mounting evidence suggests that microcirculation is a key player of SARS-CoV-2-induced pathophysiology. The angiotensin-converting enzyme type 2 (ACE2) is described as the receptor required for the viral particle cell entry [33]. This process involves priming of the viral surface spike (S) protein by the host cell serine protease TMPRSS2, as a prerequisite for cell and viral membrane fusion [33]. In addition, viral S protein has been demonstrated to induce downregulation of ACE2 [34]. These findings, together with the previous demonstration of ACE2 and TMPRSS2 expression in endothelial cells [35,36], along with other molecules involved in viral infection [37], provide a pathophysiological mechanism to support the hypothesis of direct viral infection of endothelial cells.

Recent autopsy studies have offered histological evidence of SARS-CoV-2 inside human endothelial cells. The study by Varga et al. evaluated post-mortem samples obtained from three severe COVID-19 patients. In one of them, electron microscopy revealed the presence of viral inclusions in kidney endothelial cells. In the other two patients, light microscopy results suggestive of endotheliitis (characterised by an accumulation of inflammatory cells associated with the endothelium, as well as apoptotic bodies) were found in samples recovered from the lungs, heart, kidneys, and small intestine [38]. The case-report study by Paniz-Mondolfi et al. analysed post-mortem specimens from the frontal lobe of a 74-year-old male patient with SARS-CoV-2 infection diagnosed by a positive nasopharyngeal swab test by real-time reverse transcription-polymerase chain reaction (RT-PCR). The transmission electron microscopy sections revealed the presence of viral particles within cytoplasmic vacuoles of brain capillary endothelial cells [39]. In addition, in the study by Menter et al., autopsy specimens obtained from the kidneys of two COVID-19 patients were analysed with electron microscopy, finding virus-like particles inside cytoplasmic vesicles of activated glomerular endothelial cells [40].

Recently, Damiani et al. presented the first in vivo evaluation of the microcirculation in patients with SARS-CoV-2 severe pneumonia [41]. The authors studied sublingual microcirculation, finding an inverse correlation between perfused vessel density and D-dimer levels. This study provided a direct association between human microvascular dysfunction and coagulopathy in severe COVID-19.

Thrombotic Disease in COVID-19

A second significant aspect of SARS-CoV-2-induced endothelial dysfunction is a procoagulant state. This phenomenon

has important consequences on the pulmonary complications of COVID-19. Post-mortem examination of COVID-19 elderly, hypertensive, obese, and male patients has shown that impaired microcirculation was characterised by pulmonary capillary alterations and the presence of capillary microthrombi [40].

The association between microvascular disease and hypercoagulability (expressed by increased D-dimer) has previously been recognised in patients with traditional cardiovascular risk factors, including diabetes [42,43]. Additionally, hypercoagulability has been shown to accompany the progression of atherosclerosis-associated endothelial dysfunction [44]. Increased D-dimer levels are frequently found among patients with COVID-19, especially in those with severe disease, and are associated with worse prognosis, including increased risk of intensive care admission, mechanical ventilation and death [45–47]. For these reasons, D-dimer monitoring may be considered valuable in decision-making and patient care, as lower mortality has been reported in patients with increased D-dimer who were treated with heparin, compared with those who were not [48].

Intravascular thrombosis has been reported in the macrocirculation and microcirculation in COVID-19. A pulmonary thromboembolic disorder may play an important role in the pathophysiology of respiratory failure in COVID-19, either as large-vessel pulmonary thromboembolism (present in 81% of the critically ill patients from the series by Klok et al. [49]) or as microthrombosis. In an autopsy study of 10 patients with COVID-19, Dolhnikoff et al. observed exudative and proliferative diffuse alveolar damage, with intense epithelial viral cytopathic effects involving the alveolar and small airway epithelium, with little lymphocytic infiltration, and presence of fibrinous thrombi in small pulmonary arterioles in areas of both damaged and preserved lung parenchyma in eight out of 10 cases. Endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries were other indicators of activation of the coagulation cascade. These pathological observations were supportive of the concept of microthrombosis in severe COVID-19 [50].

Escher et al. [51] reported a case of a patient with COVID-19 complicated with acute respiratory distress syndrome (ARDS) and greatly increased von Willebrand factor (VWF), who improved after full anticoagulation. The increased VWF suggested massive endothelial stimulation and damage, with release of VWF. Magro et al. described five individuals with severe COVID-19 and complement-mediated microvascular injury, which was noted in the lungs and/or skin [52]. All patients had ARDS and three also had purpuric skin lesions. Of note, patients did not display classic histopathological features of ARDS, but pulmonary findings included significant deposits of complement components in the microvasculature. The pulmonary abnormalities were largely restricted to alveolar capillaries, indicating a thrombotic microvascular injury that would explain the increased dead space fraction, with respiratory failure accompanied by greater lung compliance and less pulmonary consolidation than in typical ARDS. The skin lesions showed a pattern of thrombogenic vasculopathy, with deposition of C5b-9 and C4d in both grossly involved and normally-appearing skin.

A remarkable clinical finding with important vascular implications in COVID-19 was studied by Liu et al. They described elevated plasma angiotensin II (Ang II) levels in COVID-19 patients when compared with healthy individuals, which positively correlated with more severe lung injury [53]. Although observed in a small sample of patients, these data suggest, in combination with the known procoagulant effects of Ang II (including stimulus of the expression of tissue factor [54]), a possible pathophysiological link between RAS imbalance and COVID-19-related intravascular thrombotic disease.

The proinflammatory actions of Ang II involve innate and adaptive immune responses [14]. Accordingly, mice chronically infused with Ang II display increased vascular oxidative stress and macrophage infiltration, cytokine production and endothelial dysfunction. All of these effects were prevented by an immunologic approach, by infusing the anti-inflammatory regulatory T lymphocytes (Tregs) [55].

RAS Imbalance and SARS-CoV-2 Infection

The RAS is an essential component of vascular homeostasis, where the key enzymes ACE and ACE2 display antagonistic actions. Ang II produced by ACE induces oxidative stress, cell proliferation and inflammation [56]. Conversely, Ang-(1-7), the end product of the enzymatic action of ACE2, is associated with antioxidant and antiinflammatory effects [57].

Renin-angiotensin system imbalance has previously been suggested in bacterial sepsis. Evaluating the plasma of septic patients, Boldt et al. found higher circulating levels of Ang II when compared with controls, which were suppressed with the administration of the ACE inhibitor enalaprilat [15]. These findings were expanded by Doerschug et al., who identified that increased Ang II and plasma renin activity in septic subjects were associated with microvascular dysfunction [16]. Literature investigating the association between viral infection and RAS is scarce. Evaluating patients with chronic hepatitis C infection, Powell et al. found an association between hepatic fibrosis and one polymorphism in the angiotensinogen gene, which was related to increased Ang II synthesis [58].

The modulation of RAS in sepsis has been evaluated as a potential therapy by different approaches in the last decade. In the study with enalaprilat mentioned above [15] with a small number of patients (n=40), there was no difference in survival rate compared with the control group. Akpinar et al. investigated the effects of the renin inhibitor aliskiren in bacterial sepsis-induced acute lung injury in rats [59]. The

authors found a reduction in plasma Ang II, which was associated with a reduction of oxidative stress markers and cytokine expression in lung tissue, including IL-6 and TNF-α. Similar results were obtained in rodents with reduced lung injury during sepsis, which was associated with plasma decrease of IL-6 and TNF-α, using the angiotensin receptor blockers (ARBs) losartan [60] and candesartan [61]. ACE2 has also been associated with the potential beneficial effects of pharmacological interventions in RAS. Imai et al. showed that the administration of recombinant ACE2 reduced lung injury in mice during bacterial sepsis [62]. In addition, the administration of ACE inhibitors and ARBs increased the cardiac expression of ACE2 and plasma Ang-(1-7) in mice [63]. Indirect clinical evidence of the potential benefits of RAS modulation in infection was provided by a meta-analysis of 37 studies, which evaluated the effects of ACE inhibitors and ARBs in the risk of pneumonia [64]. The authors found that ACE inhibitors reduced the risk of pneumonia and pneumonia-related mortality, a benefit that was extended to high-risk patients, including those with heart failure and stroke.

Evidence suggesting a coronavirus-induced imbalance between ACE and ACE2 actions was previously provided by Kuba et al., who demonstrated, in the airways of mice that had been exposed to the related virus SARS-CoV, that ACE2 downregulation was associated with a local increase of Ang II [34]. Clinical studies with COVID-19 patients have demonstrated that blood levels of TNF-α and IL-6 are increased and positively correlate with disease severity [65]. Both cytokines are associated with endothelial barrier breakdown in sepsis [66] and reduced by Ang-(1-7) [67].

This working hypothesis of the vascular effects of SARS-CoV-2 is even more relevant in view of clinical evidence from cohorts in at least three continents identifying cardiovascular disease and particularly hypertension as important risk factors associated with worse prognosis of COVID-19 [68–70]. Indeed, in hypertensive patients, RAS was found to be imbalanced towards ACE activation [71], with ACE and Ang II expressed in higher levels in vascular tissues of patients exposed to cardiovascular risk factors [72].

Considering the preliminary and fast growing amount of available experimental and clinical evidence, endothelial dysfunction may occur as a direct effect of the tropism of SARS-CoV-2 for vascular tissue, inducing or potentiating a previous imbalance (as in cardiovascular and metabolic disease patients) of intracellular RAS. These phenomena, together with pre-existing endothelial injury that accompanies comorbidities – such as hypertension, diabetes, coronary artery disease, and obesity – may predispose to more severe presentations, faster evolution and worse prognosis of the disease. As the ultimate result, extensive endothelial cell damage ensues, with organ dysfunction and circulatory collapse. A schematic representation of the mechanisms proposed for COVID-19 pathophysiology regarding RAS and microcirculation is shown in Figure 1.

Research Perspectives

The interplay between RAS and the microcirculation in SARS-CoV-2 infection brings up the opportunity of exciting research perspectives. It is vital to understand the dynamics of microcirculatory function during the clinical evolution of COVID-19, with particular interest in the largely unknown initial oligosymptomatic stage. Early signs of endothelial dysfunction were previously identified in human microcirculation, days before the clinical diagnosis of bacterial disease [73]. Indeed, a timely therapeutic action in the early phase is a key principle of sepsis management [74]. As a consequence, microcirculation evaluation, which can be performed at the bedside with non-invasive methods [75], may offer important clinical data regarding prognosis and treatment effects [76].

Another important issue in current comprehension of COVID-19 is to further investigate preliminary reports of young patients without known risk factors presenting severe disease, with vascular manifestations including stroke [77]. A number of pathophysiological mechanisms are proposed regarding this complication and should be subject of future research. These include direct central nervous system endothelial infection [39], cytokine-induced local microcirculatory dysfunction [78], and the development of antiphospholipid antibodies [79].

It was previously known that ACE polymorphisms are associated with vascular complications such as diabetic nephropathy [80]. Furthermore, combinations of polymorphisms of both ACE and ACE2 have been associated with the susceptibility of developing hypertension [81]. Another recent finding was reported by Bunyavanich et al., who found an age-dependent expression of ACE2 in nasal epithelial cells of COVID-19 patients, with adults displaying higher levels than children [82]. To quantitatively or qualitatively evaluate RAS-related genes and peptides in COVID-19 patients and their association with disease progression are attractive research possibilities.

The contribution of RAS in COVID-19 is also being studied with therapeutic goals. There are 33 ongoing studies currently registered in clinicaltrials.gov evaluating interventions exploring the RAS axis, including ACE inhibitors, ARBs and Ang-(1-7) as treatment strategies (accessed 22 July 2020 at https://clinicaltrials.gov/). The imbalance of Ang II/Ang-(1-7) favouring the former in face of reduction of ACE2 activity after binding of the coronavirus suggests the possibility of beneficial effects of blockade of the angiotensin type I receptor with angiotensin receptor blockers.

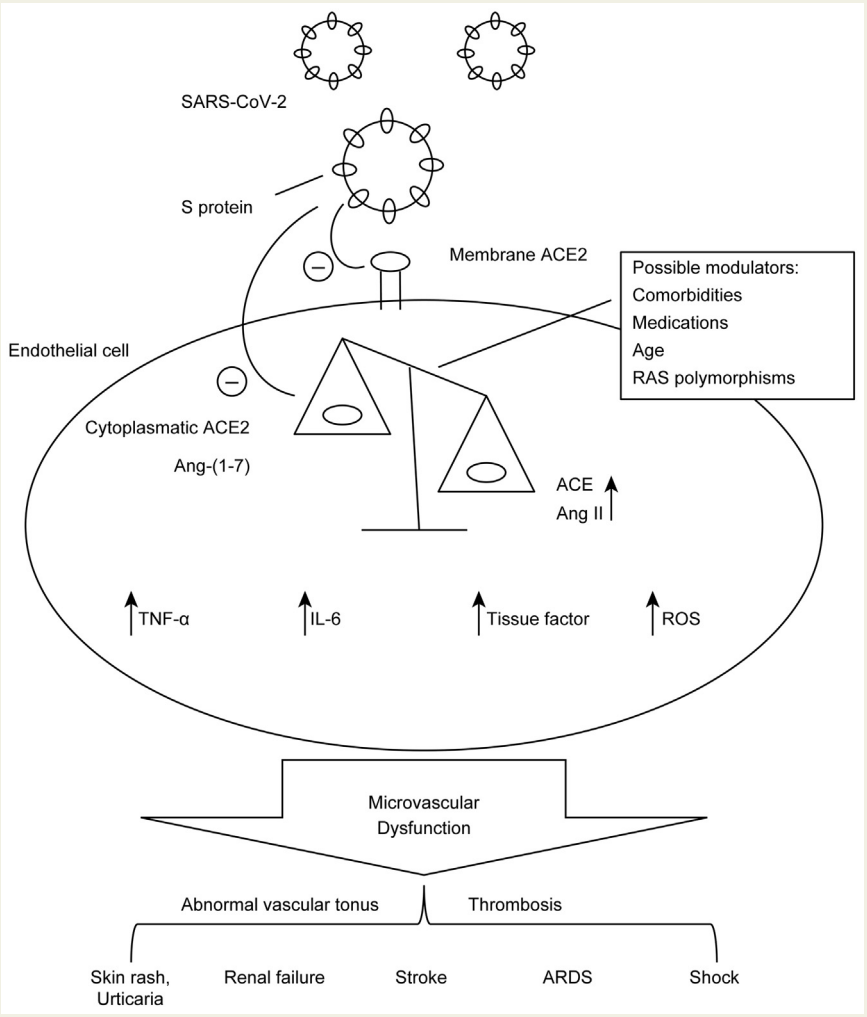

Figure 1 A schematic representation of mechanisms proposed for COVID-19 pathophysiology regarding the renin-angiotensin system.
Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme type 2; Ang-(1-7), angiotensin-(1-7); Ang II, angiotensin II; ARDS, acute respiratory distress syndrome; IL-6, Interleukin-6; RAS, renin-angiotensin system; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S protein, spike protein; TNF-α, tumor necrosis factor-α.

Conclusion

At present, the scientific community is beginning to understand the pathophysiology of COVID-19. The RAS is a powerful homeostatic system, developed in the evolutionary process hundreds of millions of years ago, allowing salt and water retention essential for vertebrates once they left their original marine environment [83], with diverse fundamental roles in health and disease. Traditionally studied in the context of chronic cardiovascular diseases, a renewed interest in RAS inflammatory and microvascular actions has been prompted by the COVID-19 pandemic. Understanding these mechanisms can lead to more effective treatments for control of this global pandemic.

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Competing Interest Statement

The authors declare that they have no competing interests.

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