A Cytokine/Bradykinin Storm Comparison: What Is the Relationship Between Hypertension and COVID-19?

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As we witness the rapidly climbing number of cases of coronavirus disease 2019 (COVID-19), clinical trials are underway for monoclonal antibody treatments and a handful of potential vaccines. Yet, nearly nine months into this deadly pandemic, the Center for Disease Control (CDC) COVID-19 Data Tracker reports that the United States is approaching 14 million cases and 300,000 deaths. Despite the growing concern about the coming winter months that will inevitably lead to elevated case numbers, there is still no clear understanding of the relationship between the severe acute respiratory syndrome of coronavirus 2 (SARS–CoV-2) and the complications observed in the renal, cardiovascular, and respiratory systems. There are currently two popular hypotheses among researchers: (i) the cytokine storm theory; and (ii) the bradykinin storm theory. From the cytokine storm perspective, upregulation of cytokines is triggering the multi-system pathological manifestations of COVID-19, including acute lung damage and respiratory distress syndrome in severely diseased patients. The newer bradykinin storm theory stresses the importance of the decreased angiotensin-converting enzyme 2 (ACE2) availability within the epithelial cells of the lungs, leading to an inability to degrade bradykinin analog, des-Arg9-BK within normal margins. ACE2 and bradykinin are both known components of the renin–angiotensin aldosterone system and now are uniquely tied into the pathophysiology of SARS–CoV-2. This sheds an interesting light on the noticeable proportion of patients that have hypertension listed as a comorbidity. The intricacies of these two hypotheses have crucial overlap that can lead to the understanding of the pathology of the SARS–CoV-2 and how it relates to the virus in severely diseased patients.

In patients that have developed severe cases of COVID-19, there is evidence of a cytokine storm. Common immune response mediators such as chemokines, leukocytes, interferons, interleukins (ILs), or tumor necrosis factors are activated. These cytokines are released in response to the viral infection and are employed to trigger and mediate the response to the viral infection. Studies have identified that the cytokine interleukin-6 (IL-6) is expressed at higher levels.[1] In addition to IL-6 and IL-1β, the IL-1 receptor is also present. This large increase of immune cell recruitment is what has been coined the cytokine storm, leading to uncontrolled inflammation and increased activation of the cytokines in question. This inflammation within COVID-19 target tissues can lead to vascular leakage and further immune cell infiltration, worsening vascular permeability and potentially leading to edema formation. The proinflammatory cytokines that are upregulated in sick patients contribute to the leaky vasculature and cell necrosis, together with antibodies that were also found to be increased during the course of the illness that have effects on cardiac function and that trigger an immune procoagulant microvascular endotheliopathy.[2] This could suggest that the cytokines follow an autoinflammatory pathway leading to the production of pro-inflammatory cytokines IL-6 and IL-18, which result in the severe pathophysiological manifestations of COVID-19.[2] Twenty-three cytokines have been identified in patients with different severity of the disease that are differentially expressed in COVID-19.[2] Other significant cytokines such as tumor necrosis factor-α and IFN-γ are also increased in patients with the SARS–CoV-2 infection.[3,4] In patients treated with the antiviral agent Remdesivir, a decrease in the levels of IL-6 in the plasma has been demonstrated.[2] The use of Remdesivir has had positive therapeutic advantages, but it has not been a dramatically effective treatment for all symptomatic patients. This could mean that there could be other significant pathways causing severe illness, and therefore there could be additional therapeutic targets.[2]

ACE2 is responsible for converting angiotensin II (Ang II) to angiotensin 1–7 (Ang 1–7), leading to opposite effects than those induced by Ang II, since the latter is vasoconstrictor and pro-inflammatory, and Ang 1–7 is vasodilator and anti-inflammatory. The downregulation of ACE2 not only increases the levels of Ang II, but it also leads to increased levels of des-Arg(9)-bradykinin (DABK) which is associated with acute lung damage and inflammation.[5] The subsequent dysregulation allows for a bradykinin storm to occur; with the lack of breakdown of DABK *via* ACE2, there will be high levels of free BK available to act on target cells (Figure 1). Bradykinin (BK) is crucial in causing vasodilation and hypotension. Rarely, there are urticarial reactions and a few cases of angioedema have been reported, mostly in patients taking ACE inhibitors, which can occur in absence of COVID-19. DABK is known to bind to not only bradykinin-1 receptors (B_1Rs), but also to bradykinin-2 receptors

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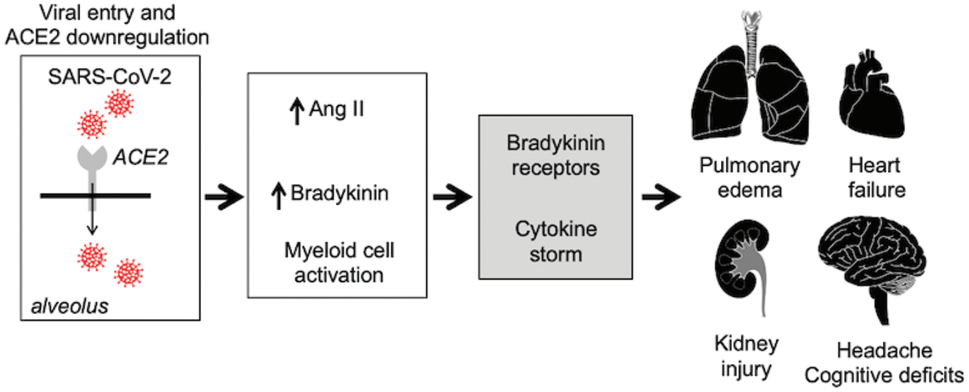
GRAPHICAL ABSTRACT



(B_2Rs) (Figure 1).[5] IL-1 and IL-6 are upregulated by SARS–CoV-2 infection, and their effects are added to the actions induced by the enhanced generation of BK in the lungs and throughout the body.[2] IL-1 and IL-6 also stimulate the expression of B_1Rs and can subsequently lead to the bradykinin storm that may be critical in the severity and wide-spread symptoms of COVID-19. Additionally, in patients who have been admitted to the ICU, there has been evidence of reduced amounts of serpin family A member 12 (SERPINA12) and dipeptidyl peptidase-4 (DPP4). These factors are normally responsible for suppression of kallikrein-mediated inflammation. However, with decreased levels of SERPINA12 and DPP4 in COVID-19 patients, the kallikrein–kinin system becomes even more active, supplementing the bradykinin storm and triggering the symptoms associated with more severe disease.[1,5] With enhanced generation of BK, the consequence will be severe multisymptomatic COVID-19 pathological changes.[6] With COVID-19 impacting the kallikrein–kinin system in a major way, there are many mediators that can influence the severity of the disease. Some of these must be addressed when discussing the impact on those patients who are hypertensive.

In the heat of the pandemic, there was growing concern about the use of ACE inhibitors in patients who became COVID positive; while this has since been discounted, there are still plenty of unanswered questions when it comes to the relationship between cardiovascular disease and COVID-19. Those who are on a regimen of ACE inhibitors are normally at risk for angioedema by an increase in BK levels. When considering the

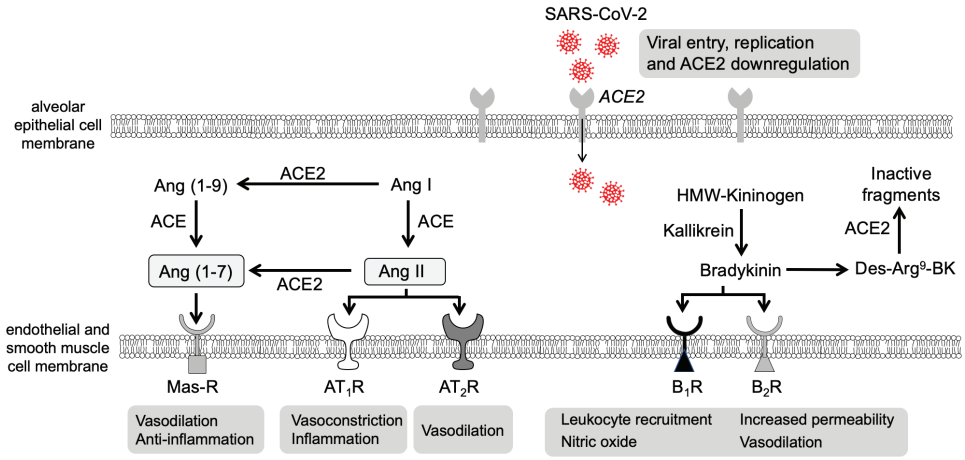


Figure 1. ACE2 is present in the alveolar epithelium and is the receptor for SARS–CoV-2 *via* the spike protein.[3] Following binding, there is decreased availability of ACE2 and therefore decreased activity. This downregulation of ACE2 by COVID-19 results in increases in the substrates of ACE2, AngII and BK.[6] COVID-19 infection also shows evidence of an increase in HA synthase 2 expression which will upregulate the production of HA and can lead to fluid retention and decreased gas permeability and acute respiratory distress syndrome often seen in COVID-19 patients.[6,8] In response to the infection, the pro-inflammatory cytokine, IL-6, is upregulated. This overexpression of IL-6 indirectly causes an increase in B1Rs on the cell surface and also indirectly causes the downregulation of SERPINA12, a suppressor for bradykinin, subsequently increasing the cell's affinity for the uninhibited bradykinin. Abbreviations: ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; AT_1R, angiotensin II receptor type 1; AT_2R, angiotensin II receptor type 2; BK, bradykinin; B_1R, bradykinin-1 receptor; B_2R, bradykinin-2 receptor; COVID-19, coronavirus disease 2019; HA, hyaluronic acid; HMW, high molecular weight; IL-6, interleukin-6; SARS–CoV-2, severe acute respiratory syndrome of coronavirus 2; SERPINA12, serpin family A member 12.[1,2]

mortality from severe cases of COVID-19, it has been reported that nearly 30% of the deaths share hypertension as a co-morbidity.[7] Additionally, within the population of patients with severe disease that experienced acute respiratory distress syndrome and died, almost 27% of those patients were hypertensive.[7]

The cytokine and bradykinin storm theories offer intriguing explanations to the diverse array of symptoms and organ systems affected after SARS–CoV-2 infection. They offer crucial novel therapeutic targets to prevent multi-organ failure in patients most severely affected by the virus, including hypertensive patients.

REFERENCES

1. van de Veerdonk FL. Netea MG, van Deuren M, van der Meer JWM, de Mast Q Brüggemann RJ, van der Hoeven H. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *eLife*. 2020;9.
2. Buszko M, Park J, Verthelyi D, Sen R, Young HA, Rosenberg AS. The dynamic changes in cytokine responses in COVID-19: a snapshot of the current state of knowledge. *Nat Immunol*. 2020;21:1146–1151.
3. Battagello DS, Dragunas G, Klein MO, Ayub ALP, Velloso FJ, Correa RG. Unpuzzling COVID-19: tissue-related signaling pathways associated with SARS-CoV-2 infection and transmission. *Clin Sci (Lond)* 2020;134:2137–2160.
4. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;203:631–637.
5. Roche JA, Roche R. A hypothesized role for dysregulated bradykinin signaling in COVID-19 respiratory complications. *FASEB j* 2020;34(6):7265–7269.
6. Garvin MR, Alvarez C, Miller JI. Prates ET, Walker AM, Amos BK, Mast AE, Justice A, Bruce A, Jacobson D. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bradykinin storm. *eLife* 2020;9.
7. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. *Am. J. Hyperten*. 2020;33(5):373–374.
8. Teuwen L-A, Geldhof V, Pasut A, Cermeliet P. COVID-19: the vasculature unleashed. *Nat Rev Immunol* 2020;20:389–391.