# SARS-CoV-2 and Hypertension: Evidence Supporting Invasion into the Brain Via Baroreflex Circuitry and the Role of Imbalanced Renin-Angiotensin-Aldosterone-System

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**ABSTRACT:** Hypertension is considered one of the most critical risk factors for COVID-19. Evidence suggests that SARS-CoV-2 infection produces intense effects on the cardiovascular system by weakening the wall of large vessels via vasa-vasorum. In this commentary, we propose that SARS-CoV-2 invades carotid and aortic baroreceptors, leading to infection of the *nucleus tractus solitari* (NTS) and paraventricular hypothalamic nucleus (PVN), and such dysregulation of NTS and PVN following infection causes blood pressure alteration at the central level. We additionally explored the hypothesis that SARS-CoV-2 favors the internalization of membrane ACE2 receptors generating an imbalance of the renin-angiotensin-aldosterone system (RAAS), increasing the activity of angiotensin II (ANG-II), disintegrin, and metalloproteinase 17 domain (ADAM17/TACE), eventually modulating the integration of afferents reaching the NTS from baroreceptors and promoting increased blood pressure. These mechanisms are related to the increased sympathetic activity, which leads to transient or permanent hypertension associated with SARS-CoV-2 invasion, contributing to the high number of deaths by cardiovascular implications.

**KEYWORDS:** SARS-CoV-2, hypertension, baroreflex, angiotensin II

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## Introduction

In March 2020, the World Health Organization (WHO) declared pandemic status due to the rapid spread of a new disease, called the coronavirus disease-2019 (COVID-19), caused by the SARS-CoV-2 virus belonging to the coronaviridae family.[1,2] SARS-CoV-2 has reached more than 200 countries, with over 250 million confirmed cases and >5 million confirmed deaths (https://ourworldindata.org/coronavirus-data, worldometers.info, and World Health Organization).[3]

Many of the severe and fatal cases are related to elderly patients or those with some comorbidity, including cardiovascular diseases (CVDs), especially hypertension, which is considered one of the most critical risk factors for the severity of COVID-19.[1,4-12] However, other studies disagree about hypertension participation as a risk factor for more ICU hospitalization and higher mortality for COVID-19.[13] Elderly patients present higher hypertension levels, increasing the risk of death when infected by SARS-CoV-2.[4,6] In China, it is estimated that the prevalence of hypertension among COVID-19 hospitalized patients in 2020 was in the range of 16.9% to 31.2%, and in the USA (data referring to New York City), this prevalence reached an alarming 56.6%; in Italy, the prevalence of hypertensive patients among patients with COVID19 who required ICU admission in 2020 was 49%.[14]

Hypertension is one of the most common cardiovascular diseases worldwide, affecting about 1.38 billion people with blood pressure equal to or greater than 140 mmHg/90 mmHg.[15] In addition, lifestyle (diet, alcohol consumption, and physical activity), age,[16] and ethnicity[15,17] are risk factors. Interestingly, the elderly and African descendants are part of the groups most

affected by hypertension, being also the most compromised by COVID-19, which indicates a possible synergistic relationship between hypertension and COVID-19.[8]

Evidence supports that CVDs and cerebrovascular diseases can influence COVID-19, facilitating the occurrence of infections, and COVID-19 can assist in the onset or worsening of CVDs.[5,6,18] SARS-CoV-2 could generate diseases of the cardiovascular system or aggravate existing pathologies due to the virus's ability to damage the vessels and the heart directly, either by activating adaptive immune and autoimmune mechanisms or by the occurrence of hypoxia due to respiratory changes or failures caused by SARS-CoV-2 infection in the lungs.[5,6,18] Similarly, other studies with viral diseases like SARS-CoV, MERS-CoV, and even influenza have shown the occurrence of similar conditions, increasing the development of severe cardiovascular diseases, heart attacks, hypertension, and mortality from cardiovascular problems as a consequence of viral infection.[1,4,6,7,18]

The mechanisms underlying the association between hypertension and COVID-19, particularly the increased severity of the condition and lethality in hypertensive patients, and the possible development of transient or permanent hypertensive conditions as an after-effect of COVID-19 remain unknown.[7,14,18] The hypothesized mechanisms include an imbalance in the renin-angiotensin-aldosterone system (RAAS) activation due to the use of the angiotensin II-converting enzyme (ACE2) by SARS-CoV-2 to enter human cells,[14,19-21] and the ability of SARS-CoV-2 to deregulate the RAAS system via immunological interference.[6]

However, when considering all symptoms related to COVID-19, especially those linked to more severe cases with a greater chance of death, it is possible to assume that these symptoms may be related to the entry of the virus into the central nervous system (CNS). Due to the expression of ACE2 in the brain,[14,20-22] several findings relate the neurotropic profile of the CoVs family viruses to the CNS.[22-24] Based on the possibility of viral invasion in the CNS, this review aims to (i) propose a new pathway for neuroinvasion that compromises the baroreflex system; and (ii) to establish the possible relationship between angiotensin II (ANG-II), a disintegrin, and metalloproteinase 17 domain (ADAM17) with the imbalance of the RAAS system that leads to sympathetic activation. Together, all these factors support the association between COVID-19 and hypertension, which can be a determining factor in patient survival.

### *SARS-CoV-2 neuroinvasion and neurofunctional implications*

The neurotropic and neuroinvasive characteristics of the CoV family viruses[23,25-27] and the occurrence of symptoms associated with CNS involvement seem to support the real possibility of SARS-CoV-2 invading the brain and spinal regions.[14,19-21,28]

Several neuroinvasion pathways for SARS-CoV-2 and other members of its family have already been proposed, such as hematological, enteric, pulmonary, olfactory, ocular, buccal (through salivary glands), and placental routes.[2,19,20,22,24,27,29-39] In addition, some authors have suggested that the element that seems to unite almost all these pathways is the apparent capacity of contamination from one neuron to another for neuroinvasion, the trans-synaptic or trans-neuronal pathway, whose viral agent is disseminated between different neurons that are connected by circuits.[20,27,30,31] The trans-synaptic pathway is used to describe the invasion of the virus in the brain through the peripheral nerves, using sensitive nerve endings located in the organs or tissues.[27,30,31] The virus can spread in the brain through these circuits and adversely affect different functions.[27,30,31]

Patients with COVID-19 have symptoms or complications related to central nervous system alterations: anosmia, ageusia, loss of movement coordination (ataxia), paresthesia, akinetic mutism, headaches, nausea, dizziness, loss or impairment of consciousness, delirium, hallucination, confusion, loss of hearing, worsening cognitive deficits, neuroinflammation of the brain and spinal cord, neurovascular inflammation and atherogenesis, neurodegeneration, loss of progressive control of respiratory function, encephalitis and encephalomyelitis, seizures, encephalopathy, neuropsychopharmacological disorders, stroke, and hypertension (especially pulmonary and intracranial).[20,22,28,30,31,40-47] A recent study analyzing several original research articles comprising neurological and neuroimaging data from patients with COVID-19 has suggested that at least one-third of the patients had brain injuries or abnormalities caused by SARS-CoV-2.[48]

The clinical symptoms that COVID-19 presents are widespread, depending on the severity of cases and tissues or organs affected by the virus.[49] It is estimated that about 35% to 40% of patients have neurological symptoms, especially in the elderly and in patients presenting severe infection[33,34,42] or those with a history of cerebrovascular, cardiovascular, renal, and liver diseases.[33,34]

When SARS-CoV-2 invades the CNS, its removal is difficult because of the lack of an antigen of the major histocompatibility complex in neurons, dense parenchyma, and characteristics of the nervous tissue that favor viral permanence for a long time.[44,50] Furthermore, an intense neuroinflammatory condition weakens the blood-brain barrier (BBB), culminating in the entry of T cells and microglial activation to "fight" the virus in the brain.[51] The combination of these factors leads to chronic neurological damage. It can also make the brain or nervous structures a reservoir of viruses that can compromise the patient's systemic condition due to the association of neural areas with the regulation of vital peripheral organs/functions.[34] Therefore, the neuroinvasion can also allow the worsening of the systemic condition of the COVID-19 patient, causing disturbances in the regulation of blood pressure with the occurrence of systemic or pulmonary

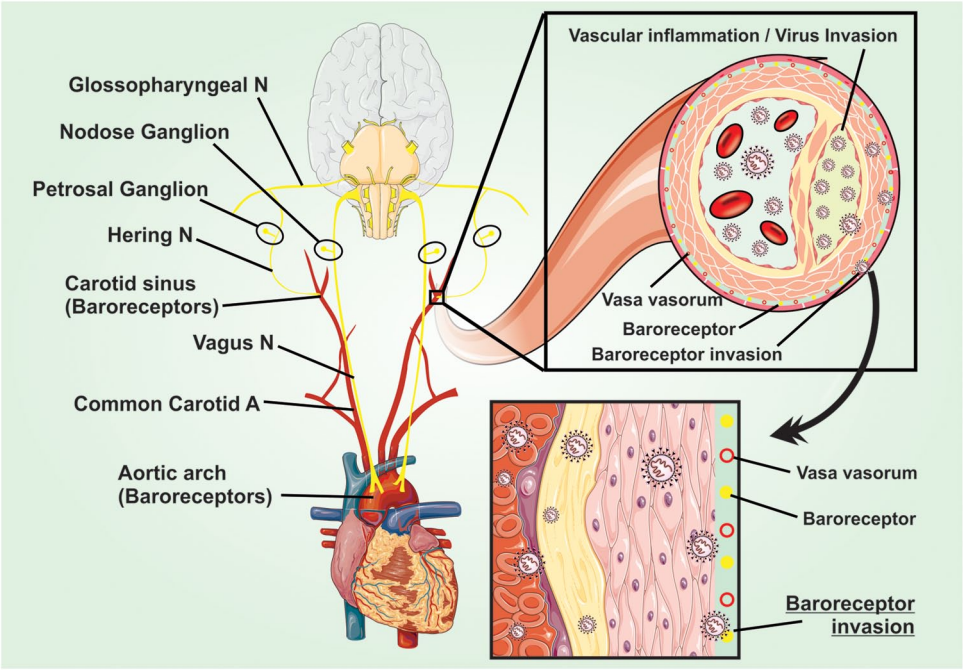


**Figure 1.** The cartoon depicts the vasculature invasion by SARS-CoV-2 by weakening vessel walls and baroreflex. In addition, the possible neuroinvasion through vagal and glossopharyngeal nerves is indicated.

hypertension that can lead to the evolution of the disease, culminating in the failure of several organs, especially when it occurs together with hyper inflammation, cytokine storm and increased systemic inflammation.[34]

Subsequently, we will discuss the hypothesis of how SARS-CoV-2 can reach the brain and lead to the worsening/generation of arterial hypertension. Many authors have argued based on animal experiments and clinical studies and hypotheses related to the capacity of neurotropism and neuroinvasion of other viruses in the same family.[6,21,32,42,55,73] Although additional studies are needed to fill the many gaps regarding the mechanism, it is crucial to understand the association between hypertension and COVID-19 for the advancement of treatment, prognosis, and especially the prevention of more severe forms of the disease.

### *SARS-CoV-2 and the baroreflex: A new neuroinvasion proposal*

Recently, clinical studies have shown an important role for the endothelium during the development of COVID-19 because of its strong relationship with the immune system, which generally determines the course of the disease.[52] Endothelial cells have high ACE2 expression and are the primary targets for SARS-CoV-2 invasion, leading to contamination of vessels, especially those with a large caliber, which may justify neuroinvasion.[49,53]

Recent studies have shown that SARS-CoV-2 infection of the endothelium increases the activity of the immune system and the interaction of its components with the vessels, resulting in endothelial damage due to the activation of defense cells and the disordered release of pro-inflammatory cytokines that contribute to the degradation and weakening of the vessel wall and apoptosis and pyroptosis of endothelial cells.[52] This scenario favors the viral entry into the deepest histological layers of the vessels, such as the connective layer, the muscle, and the adventitia, either indirectly, through the contamination of the vasa-vasorum by SARS-CoV-2 (as seen in cases of Kawasaki disease associated with COVID-19)[54] or directly, by the action of pro-inflammatory cytokines that could damage the vessel wall.[55] Thus, profound vascular changes, including in large-caliber vessels, resulting from COVID-19 may be associated with the following factors: (i) endothelial inflammation[56]; (ii) endothelial damage, which changes the vascular balance and generates vasoconstriction, ischemia, thrombus formation, and inflammation associated with edema[57]; (iii) vasculitis[58]; (iv) formation of thrombus in large vessels (aorta) due to the formation of neutrophil extracellular traps (NETs) and changes in the functioning of platelets and pro-coagulating factors.[13,23-25,55,59,71] Because of the weakening of the vessel wall and possible viral penetration, the virus can access nerve structures within the vessels, such as the aorta and the common carotid artery, which have neural circuits that integrate these vessels into the nucleus of the solitary tract (NTS) (Figure 1).

Carotid chemoreceptors have been suggested as possible loci for SARS-CoV-2 entry into the brain via neuronal afferents (such as glossopharyngeal) to the NTS.[36] Recent studies have associated the carotid chemoreceptors affected by SARS-CoV-2 with silent hypoxia, suggesting the virus acts by decreasing baroreflex sensitivity.[60,61] Such alteration is linked to local inflammation caused by the virus, leading to baroreceptors' breakdown and their function.[36] We hypothesize that

SARS-CoV-2 neuroinvasion also occurs via aortic baroreceptors using the entire baroreflex structure.

Endothelial damage resulting from an over-stimulation of the immune system[52] and the invasion of SARS-CoV-2 via vasa-vasorum[54] can disrupt the vessel, allowing the penetration of the viruses and their contact with baroreceptors. Disruption of baroreceptors likely explains the relationship between hypertension and COVID-19 because baroreceptors are directly related to blood pressure control (BP). The baroreflex likely provides a trans-synaptic transmission pathway for SARS-CoV-2 to invade the CNS and compromise sensitive nuclei involved in cardiorespiratory control.

Baroreceptors, the nerve endings linked to elastic connective tissue fibers of collagenous origin, are in specialized portions of the tunica media and adventitia of large vessels. They are sensitive to stretching and are located mainly at the bifurcation of the common carotid artery and the aortic arch.[62,63] This system acts as an autonomic pacemaker and strictly regulates BP. Baroreceptors have cell bodies in the petrosal and nodose ganglia, projecting central endings to the NTS and distal endings to the walls of the great vessels.[62-64] The increase in blood pressure stretches the artery wall, which leads to depolarization of the distal terminations of the baroreceptors and stimulates the NTS via the vagus nerve (aortic baroreceptors) or glossopharyngeal nerve (carotid chemoreceptors). The efferents emerging from second-order neurons in NTS will orchestrate sympathetic and parasympathetic output to return BP to normal levels.[62-64]

Autonomic modulation occurs in 2 main ways. (i) The parasympathetic-excitatory pathway is formed by NTS projections to the nucleus ambiguous (NA) and the dorsal motor nucleus of the vagus (DMV). The excitatory stimulation of this pathway increases parasympathetic activity in the heart, promoting bradycardia and resulting in decreased cardiac output, which, in turn, lowers the blood pressure inside the vessels.[62,63] (ii) The sympathetic-inhibitory pathway is formed by the glutamatergic projections from NTS to the caudal ventrolateral medulla (CVLM), which, in turn, emit inhibitory projections to the rostral ventrolateral medulla (RVLM), where most of the presympathetic neurons are located. CVLM neurons release GABA in RVLM and hyperpolarizing spinally-projecting presympathetic neurons that control vasomotor function. As a result, the inhibition of sympathetic outflow to the vasculature decreases peripheral resistance, and consequently, BP. In addition, the baroreflex-mediated inhibition of RVLM neurons also suppresses the sympathetic outflow to the heart (decreasing contraction force and cardiac output) and the adrenal glands (decreasing the release of epinephrine into the circulation) both effects contributing to the lowering of BP.[64-66] Besides modulating RVLM presympathetic neurons, the baroreflex can regulate sympathetic activity through connections with the paraventricular nucleus of the hypothalamus (PVN). The PVN contains presympathetic neurons and controls sympathetic activity by sending direct projections to the intermediolateral cell column of the spinal cord (exciting preganglionic sympathetic neurons) or via excitatory projections to RVLM presympathetic neurons. The PVN also establish connections with the NTS, which stand out because their cardiovascular afferents bring information to the CNS capable of modulating the PVN response.[67] Thus, baroreflex activation can also inhibit sympathetic outflow through the modulation of PVN presympathetic neurons, affecting peripheral resistance, cardiac output, and the release of catecholamines from the adrenal glands and contributing to normalizing BP levels.[64,68] The dysfunction of baroreflex mechanisms has been reported to contribute to neurogenic hypertension since the inhibitory modulation of RVLM, and PVN presympathetic neurons are compromised, leading to sympathetic overactivity and elevated BP. Therefore, we hypothesized that SARS-CoV-2 invades neurons through vessels via the weakening of the wall of large vessels and with the possibility of contamination via vasa-vasorum in the adventitia layer, accesses the baroreceptors located in the carotid artery and aortic arch. The baroreflex circuitry can promote the access of the virus to the NTS via the vagus and glossopharyngeal nerves, deregulating blood pressure at the central level (Figure 2).

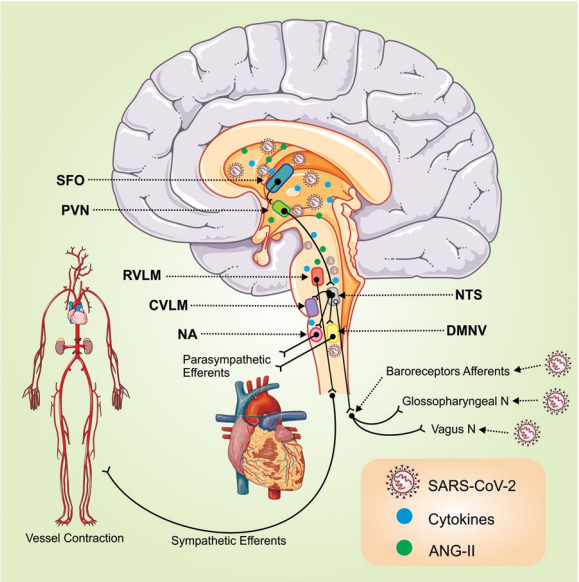


**Figure 2.** The cartoon illustrates the possible SARS-CoV-2 neuroinvasion through baroreceptor circuitry. Increased Ang-II and cytokine levels in the brain, as a consequence of viral infection, damage the endothelium and disrupt BBB, which adversely affects the function of brain nuclei controlling blood pressure (SFO, PVN, NTS, NA, RVLM, CVLM) and impairments in heart and the control of hypertension in blood vessels.

### *SARS-CoV and unbalance in RAAS: Alteration of the baroreflex and promotion of neurogenic hypertension*

The control of BP is a complex and refined process performed by the nervous, endocrine, and renocardiovascular systems.[69] Traditionally, RAAS has been described as an endocrine system

that controls vascular function, hydroelectrolytic balance, blood pressure, and peripheral vascular resistance.[70-76] RAAS plays an important role peripherally in different organs such as vessels, kidneys, heart, adrenal gland, and intestine.[36,70,77] In addition, RAAS acts on the CNS through 2 components, ANG-II and ACE2. ANG-II is an activator molecule of RAAS, described as a peptide composed of 8 amino acids. As it does not cross the BBB, the ANG-II is only able to access central structures from the circumventricular organ (CVO), especially from the subfornical organ (SFO), due to the absence of BBB from these brain structures.[20,78,79] ACE2 is a molecule that inhibits RAAS activity and is described as a protein widely expressed in the brain, such as SFO, PVN, NTS, NA, NMDV, RVLM, and hippocampus. Many of these brain areas are related to central BP control.[19,20,41,70,80]

Lately, it was discovered that RAAS promotes and maintains the inflammatory response and plays a role in the manifestation of many diseases.[81-83] The RAAS imbalance has been critically associated with SARS-CoV-2 infection,[20,70,77] possibly due to the high affinity of this virus to ACE2, being 10 to 20 times higher than the affinity of SARS-CoV.[36] Interestingly, some of the conditions that compose the main comorbidities of COVID-19, which are associated with the development of more severe conditions and a greater chance of death, such as obesity, diabetes, cardiovascular diseases, hypertension, kidney, and lung diseases, are conditions that have, to a greater or lesser degree, their pathophysiology influenced by the unbalance of the RAAS.[77] Not by chance, these diseases or conditions are also characterized by the strong presence of chronic inflammatory processes.[77,84,85] Elevated levels of inflammation have also been recorded in patients with moderate and severe cases of SARS-CoV-2 infection. Such inflammation is related to CNS damage, and a worse prognosis is associated with a greater chance of death from COVID-19. Thus, some studies suggest that alleviating inflammation following SARS-CoV-2 infection improves the general condition of patients and decreases the risk of death.[51]

The influence of SARS-CoV-2 on RAAS unbalance likely occurs due to the internalization induction effect of membrane ACE2 receptors after virus entry into cells.[8] This effect promotes an increase in ANG-II/AT1R levels concerning ACE2/Ang(1-7)/MasR levels since the conversion of ANG-II to Ang (1-7) is made by the action of ACE2.[8] Thus, the lower availability of ACE2 reduces the conversion of ANG-II, making it more prevalent (Figure 3A and B). Therefore, the effects related to ANG-II mediated by AT1R activation are exacerbated. The AT1R receptor is expressed in brainstem areas, such as in RVLM, increasing sympathetic activity and blood pressure, which may indicate a possible relationship of AT1R with the development of neurogenic hypertension and changes in baroreflex sensitivity.[8,84-86]

Among the effects of ANG-II, its effect on the $AT_1R$ receptor is in addition to the already-known vasoconstrictor effect.[86,87] There are several other effects with a direct influence

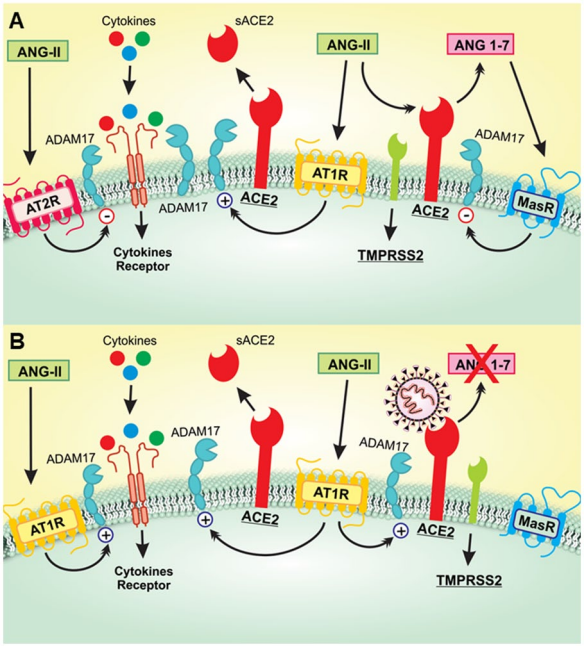


**Figure 3.** The cartoons depict the renin-angiotensin-aldosterone system (RAAS) homeostasis and imbalance. (A) RAAS homeostasis is characterized by a balance between molecules and receptors responsible for proinflammatory (ANG-II, AT1R, ADAM-17) and antiinflammatory (ANG 1-7, MasR, and AT2R) responses. (B) The RAAS imbalance caused by SARS-CoV-2-ACE2 results in increased AT1R and ADAM17 activity, exacerbating the proinflammatory response. In addition, this disorder releases sACE2, compromises ANG 1-7 formation, and reduces MasR and AT2R activity.
Abbreviations: ACE2, angiotensin converter enzyme 2; ANG-II, angiotensin II; ANG 1-7, angiotensin 1-7; AT1R, angiotensin receptors 1; AT2R, angiotensin receptors 2; MasR, macrophages receptor; sACE2, soluble angiotensin converter enzyme 2; TMPRSS2, transmembrane serine protease 2.

on pressure control. One of the most described is the elevation of ROS production because of their activating action on the enzyme dinucleotide phosphate oxidase nicotinamide adenine [NAD (P) H]. The increase in oxidative stress would lead to an increase in the action of chemokines, which would activate and attract T cells. These cells, in turn, would infiltrate key organs such as the heart, and help to generate hypertension.[86,87] In the CNS, the increase in ROS levels and oxidative stress in SFO, PVN, and RVLM are related to hypertensive conditions. In addition, it has been recorded that oxidative stress in areas such as CVO, hypothalamus, and brainstem can trigger cardiovascular problems.[86,88] Hypertension caused by ANG-II elevates the level of ROS, but hypertension induced by norepinephrine does not infer this parameter, indicating a characteristic effect of ANG-II.[86,88]

It has been described that the increased activity of enzymes involved in the production of ROS can disconnect NTS and NA, leading to loss of baroreflex sensitivity.[65] Consistent with this concept, studies have shown that antioxidant treatment administrated systemically or directly into RVLM and SFO can reduce hypertension.[86]

Additionally, ANG-II promotes the inflammatory response via the activation of defense cells. Previous studies have shown

that ANG-II plays a chemoattractant role in defense cells and induces endothelial and smooth muscle cells to release cytokines, P-selectins, and adhesion factors, resulting in the attraction and adhesion of monocytes and neutrophils to vessels.[70] Furthermore, ANG-II acts on helper and cytotoxic T lymphocytes (which can express not only the $AT_1R$ receptor but also release the Ang II itself), acting with an autocrine profile in cell activation, proliferation, differentiation, migration, and adhesion. The activation of leukocytes, in turn, causes vascular inflammation and renal and vascular hypertension.[70,87,88] The stimulation of defense cells weakens the BBB, facilitating the entry of T cells and ANG-II circulating in the CNS and increasing neurological damage.[25,30,31,68,89]

Another factor that associates ANG-II with a comprehensive inflammatory response is the ANG-II-induced release of pro-inflammatory chemokines and cytokines (IL-1β, IL-6, TNF-α, TGF-β, MCP-1 INFγ); and inhibition of anti-inflammatory cytokines, especially IL-10, in central autonomic regions that control BP, such as PVN and RVLM.[87,88] The increased inflammatory status induced by ANG-II within the PVN and the RVLM have been associated with a vasomotor sympathetic tone, which contributes to hypertension.[87,88] Effects of the production of these cytokines and the alterations in immune pathways affect kidneys and the heart, contributing to the fibrosis response of peripheral structures and the development of CVDs. The increase in peripheral cytokines can even exert effects in central areas, such as SFO, because it does not have BBB[20] and lead to the development of hypertension, suggesting that, even if neuroinvasion does not occur, peripheral effects of SARS-CoV-2 infection, as the increase in the arrival of ANG-II and cytokines, can trigger the hypertensive response via central mechanisms, which implies the possibility of direct or indirect action of this virus in the pressure control structures.[87] It is important to consider that the anti-inflammatory mediators of the RAAS pathway are reduced because there is a low conversion of ANG-II into Ang(1-7).[87]

ANG-II also appears to act on microglia. Rats with ANG-II-induced hypertension showed an increase in microglial activation, either due to microgliosis or the increase in pro-inflammatory cytokines generated by ANG-II. Increased microglial activation has been associated with increased neuroinflammation and expression of glutamatergic receptors in the PVN. This configuration can favor the activation of this nucleus and reduce the threshold for firing in these neurons, activating the entire sympathetic excitatory pathway, promoting, among other effects: the increase in plasma vasopressin levels and an increase in BP.[87,88] Along with the effects on the PVN caused by ANG II-induced microglia activation, there are the effects caused by the ANG II itself on this nucleus. In vitro studies demonstrated the action of ANG II on the 2 main classes of PVN neurons via AT1R: the parvocellular neurons (which control sympathetic activity) and the magnocellular ones (which synthesize oxytocin and vasopressin and secrete them at the neurohypophysis). However, while parvocellular neurons directly respond to ANG II, magnocellular neurons can also respond directly or indirectly, depending on excitatory (glutamatergic) stimulation coming from other neurons around the PVN.[90,91] Thus, it is possible that an imbalance in the RAAS promotes changes in the 2 main PVN neuronal populations, contributing to the pathological scenario described here.

Changes in astrocytes due to the action of ANG-II have also been recorded. Astrocytes regulate neuronal and neurohumoral function in hypothalamic nuclei such as PVN and supraoptic nucleus (SON). The release of glutamate in the extracellular space in nuclei such as PVN may evoke a persistent activation of NMDA receptors. Astrocytes determine the magnitude of this activation through the glutamate transporter 1 (GLT1) expression. However, it was found that ANG-II can modulate this process since it can block GLT1 from astrocytes, preventing the uptake of glutamate by these cells.[68] Such an effect leads to elevated glutamate levels and an overexcitation of the PVN sympathetic excitatory pathway, especially in extrasynaptic neurons that project to the RVLM. The excitation of this bulbar nucleus is associated with increased BP and contributes to the installation of the condition of neurogenic hypertension.[68]

ANG-II also modulates the integration of afferents that reach the NTS from the baroreceptors, which can increase pressure. Such effect is due to the ability of ANG-II to promote an increase in GABAergic neurotransmission, skewing afferent transmissions from baroreceptors to second-order neurons in NTS, which stands out not only for expressing both $AT_1R$ and ANG-II itself but also for being a nucleus sensitive to GABA modulation.[66] The high sensitivity of NTS to GABA may be associated with many GABAergic neurons, nerve endings, and type A and B receptors, which reduce the effects of ANG-II or increase the BP induced by intracerebral administration of ANG-II, respectively.[66]

Furthermore, recent studies show that GABA and ANG II can alter the sympathetic tone when interacting in the NTS, indicating the participation of GABA in the control of cardiovascular function. NTS is described as an indirect inhibitor of RVLM, acting via CVLM. Therefore, NTS can be inhibited by the release of GABA induced by ANG-II/AT1R, which can decrease the baroreflex sensitivity and lead to an increased BP due to the inhibition of baroreceptor signals and RVLM upregulation.[66]

Activation of ADAM17 is another factor in the pathophysiology of SARS-CoV-2. ADAM17, a disintegrin and metalloprotease of the ADAM family, is also known as tumor necrosis factor-α converting enzyme (TACE).[8,87] ANG-II activates AT1R and promotes upregulation of ADAM-17, which leads to increased shedding of ACE2 due to cleavage and release of its ectodomain. Such an effect leads to reduced expression of ACE2 on the cell surface and increased release of its soluble free form (sACE2).[8,87] In addition, ADAM17 can

cleave more than 80 molecules, which is associated with the dysregulation of immunological cytokines.[87]

ADAM17 is widely expressed in vessels, the heart, kidneys, testes, lungs, spleen, muscles, and brain, contributing to hypertension at peripheral and central levels.[8,87] Peripherally, ADAM17 promotes the transactivation of the epidermal growth factor receptor (EGFR), induced via Ang II, and can generate hypertrophy in vascular musculature, contributing to hypertension and other cardiovascular diseases. At the central level, the activation of ADAM17 contributes to the development of a hypertensive condition from the invasion of defense cells in the CNS, activation of microglia, and production of cytokines in the CNS (such as TNF-α, making it challenging to produce the enzyme glutamic acid decarboxylase (Gad) and, therefore, GABA) and neuroinflammation.[8,87]

However, its action in controlling sympathetic activity, specifically in PVN, draws the most attention when analyzing the influence of ADAM17 in conditions such as neurogenic hypertension and changes in baroreflex sensitivity. These conditions seem to be directly influenced by the ACE2 shedding performed by ADAM17 since ACE2, when converting ANG-II to Ang (1-7), plays a fundamental role in the inhibitory control of PVN, given the necessary stimulation of Ang (1-7) for the formation of GABA. Thus, without ACE2, the inhibitory control of this nucleus is impaired, and the firing of glutamatergic neurons increases, thus promoting an increase in sympathetic activity. ADAM17 expression in glutamatergic neurons is related to decreased regulation and strength of GABA receptors, reducing inhibitory control over this group of GABAergic neurons.[92] Therefore, ANG-II is directly or indirectly related to the increase in glutamate levels, which intensifies the activation of the sympathetic pathway, and to the reduction of GABA levels in the PVN and RVLM, which contributes to the increase in BP.[93]

Because of its presence in the CNS, ANG-II/ADAM17 may be related to the pathophysiology of SARS-CoV-2. ADAM17 is considerably more expressed in the brain than TMPRSS2,[25] which provides greater importance to ADAM17 in developing SARS-CoV-2 infection, and in the relationship of COVID-19/brain. Therefore, increased ADAM17 in the CNS could contribute to neurotropism and neurovirulence in the viral neuroinvasion of SARS-CoV-2.[25]

Besides ACE2, the virus entry into the cell is conditioned by other molecules, like proteases, such as TMPRSS2.[25] ADAM17 acts as a viral cofactor and competes with TMPRSS2 in the "shedding" of ACE2. The cleavage of TMPRSS2 does not produce an active molecule, unlike ADAM17, whose shedding produces sACE2 capable of counterbalancing the action of ANG-II, which could potentially block or reduce viral circulation.[8,70,94] However, beyond this assumption, sACE2 is associated with increased blood pressure[95] and the activation of defense cells, which can contribute to worsening the immune system's imbalance,[70] especially in patients who already have conditions that directly or indirectly affect this system.

Some publications propose that the production of sACE2 would have a protective effect against SARS-CoV-2. However, in the SARS-CoV epidemic, the downregulation of ADAM17 decreased the viral infection. Therefore, sACE2 was not responsible for the decrease in the action of this viral agent.[25] It is believed that something like this could also happen with SARS-CoV-2.[25] This perspective agrees with recent findings demonstrating that SARS-CoV-2's entry into cells is facilitated after the ACE2 receptor's cleavage. Also, the shedding activity can help promote the expression of molecules involved in this process, such as ADAM17.[25]

Furthermore, it was observed that in pulmonary epithelial cells of patients infected with SARS-CoV-2, ADAM-17 activity could be reduced by an inhibitor of tissue metalloproteinases 3 (TIMP3). Such results imply that the action of SARS-CoV-2 on cells significantly affects the expression and action of TIMP3, resulting in increased activity of ADAM-17. In the lungs, the increasing activity of ADAM-17 is related to the development of fibrotic tissue and an increase in infection.[19] Although much remains to be understood, it is believed that ADAM17 inhibitors can play a protective role in the infection by reducing the shedding of ACE2, reducing the infectivity of the virus,[96] and the inflammatory condition.[70] Such inference is supported by a study in an animal model demonstrating that ADAM17 inhibitors (such as apratastat and TMI-1) can prevent the progression of COVID-19's severity by preventing lung injury caused by the invasion of neutrophils.[97] The action of ADAM17 favors the production of the active form of TNF-α, which is strongly linked to critical events, such as cytokine storms and neutrophil recruitment (both linked to the most severe cases of COVID-19). Thus, the inhibition of ADAM17 decreases the levels of pro-inflammatory cytokines and endothelial adhesion molecules (necessary for the migration of defense cells from vessels to tissues affected by the infection), as well as the infiltration of neutrophils, attenuating lung inflammation and improving the overall outcome.[97]

ADAM17 has broad implications for the brain. The phenomenon seen in pulmonary epithelial cells could also occur in neuronal and glial cells. Thus, the increased activity of ADAM17 in the brain could contribute to neuronal damage and alterations in the neuroinflammatory response, which can cause many neurological symptoms observed in COVID-19 patients. Recent evidence demonstrates that the inhibition of ADAM17 following cortical brain injury promotes new neuron production and repair. The action of ADAM17 is, therefore, directly involved in altering the differentiation of neural progenitor cells into neurons (neurogenesis). Indeed, ADAM17 has been shown to facilitate the differentiation of neural precursors into glial cells, actively contributing to the formation of a glial scar. In addition, ADAM17 impacts the migration of newly formed neurons from neurogenic zones to the damaged cortical areas and neuronal survival by releasing cytokines and other molecules that contribute to neurodegeneration.[98]

Hypertensive patients display elevated ADAM17 and reduced ACE2 expression, especially in the brain.[95] ADAM-17 inhibition could attenuate inflammation and hypertension.[87,99] Furthermore, from its involvement in the comorbidities and pathophysiology of COVID-19, ADAM17 inhibition can potentially block severe SARS-CoV-2 infection.[97] Thus, elevated ADAM17 is likely the cause of the severe COVID-19 associated with neurological symptoms in hypertensive people. Moreover, the worsening of hypertension and multiple neurological symptoms in COVID-19 patients is likely a result of intense activation of ANG-II and ADAM17.

The loss of blood pressure control can also lead to neurological sequelae, which could be caused by different events, including damage to specific neural circuits, especially the GABAergic neurotransmission in the PVN and NTS, in addition to effects directly linked to ANG-II activity, such as increased levels of ROS and oxidative stress, activation of defense cells, BBB damage, alterations in the GABA-ergic and glutamatergic neurotransmission in different nuclei of the medulla and the hypothalamus. Collectively, the factors described above support our hypothesis of the direct involvement of SARS-CoV-2 in the development or worsening of the hypertensive[100,101] response by influencing the baroreflex and/or the PVN-driven neurogenic hypertensive response. Additionally, other studies have associated hypertension after immunization against COVID-19 using different immunizers.[102-106] However, because of many controversies and obscure points on this topic, more studies targeting these issues are needed to understand the mechanisms involved.

## Conclusion

This commentary proposes a new route of neuroinvasion by which the virus systematically acts to promote hypertensive conditions in many COVID-19 patients. While many issues regarding neuroinvasion, neurotropism, and neurovirulence, and the neurological effects of SARS-CoV-2 are still under investigation, the available evidence supports our hypothesis.

## Author Contributions

Conceptualization: OWC and KBO; Formal analysis and Investigation: KBO, BRMS, OWC and KLSO; Project administration and Supervision: OWC and AKS; Roles/Writing—original draft: KBO, ISS, and OWC; Writing—review & editing: RSS, ISS, LA, PLK, VRS, AKS, and OWC.

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