Conceptual Article

Interaction between SARS-CoV-2 and the Renin Angiotensin system

Interação entre SARS-CoV-2 e o sistema Renina Angiotensina

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Introduction

COVID-19 or SARS-CoV-2, as the International Virus Taxonomy Committee[1] Coronavirus Study Group has called it, is a disease caused by betacoronavirus of the same subgenus as severe acute respiratory failure syndrome (SARS)[2]. In August 2020, the pandemic spread to more than 188 nations, causing more than 21.4 million people infected and over 771,000 fatalities worldwide[3]. The World Health Organization provides updated data, confirming more than 47.9 million cases of SARS-CoV-2 and 1,290,653 deaths by November 15 2020[4].

SARS-CoV-2 is a spectral disease whose clinical status of those infected may vary from asymptomatic to death. In the absence of a classification based on symptoms, we propose a clinical classification divided into five stages, described in Chart 1.

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Chart 1. Clinical classification of SARS-COV-2

Stage	Clinical Characteristic
I	Contaminated but asymptomatic.
II	With mild flu-like symptoms: fever, inflammation, sore throat, joint pain, anosmia, dysgeusia, and dry cough. You only need care for the common flu. It corresponds to 80% of the cases.
III	With flu-like symptoms associated with acute respiratory distress or acute respiratory syndrome, with or without cardiac and/or renal complications, requiring health care of medium complexity.
IV	With flu-like symptoms, an acute respiratory syndrome-associated or not with cardiac complications and/or acute renal failure, in need of highly complex health care.
V	Cardiorespiratory complications that culminate in death. It represents between 2 to 4% of cases.

Mortality caused by SARS-CoV-2 is associated with the following factors: Diabetes Mellitus, Systemic Arterial Hypertension (SAH), Coronary Artery Disease, and age over 70 years (the only non-modifiable factor)[5]. The inflammatory process is also associated with mortality after infection by SARS-CoV-2. High inflammatory markers, such as C-Reactive Protein and Interleukin-6, were predictors of a worse prognosis[1].

According to the pathophysiology previously described, SARS-CoV-2 penetrates human cells through the same receptors as Angiotensin-Converting Enzyme 2 (ACE 2). ACE 2 is an enzyme that makes up the Renin-Angiotensin System (RAS), is expressed mainly in the arterial endothelium of coronary arteries and intra-renal vessels, in pulmonary epithelial tissue and enterocytes[6,7]. Understanding the interaction of SARS-CoV-2 with RAS is of great importance for the most different health professionals' performance. Therefore, in this article, we aim to describe in-depth the RAS and later the interaction between SARS-CoV-2 with this system. In this way, we seek to elucidate some questions that are still poorly understood about the disease and raise some hypotheses based on the exposed context that may guide future investigations.

Renin-Angiotensin System

RAS can be divided into systemic and tissue. The production of angiotensins that act on the different body tissues (systemic RAS) has the liver, kidneys and arterial vascular endothelium as protagonists, being an endocrine hormonal system. Tissue RAS, on the other hand, acts in an autocrine and paracrine manner. All the components of the RAS are produced locally in the heart, brain, arterial blood vessels (endothelium), kidneys, adrenal glands, reproductive organs, pancreas, and adipose tissue[7-9]. As the systemic and tissue RAS are homologous, we will specifically describe the systemic pathway, reporting when necessary, to the tissue pathway.

The main constituent molecules of this system are angiotensinogen, angiotensin I, II, III, IV, and I-VII, angiotensin-converting enzymes 1 and 2 (ACE 1 and 2), and angiotensin receptors 1, 2, 4, and 1-7 (AT1, AT2, AT4, and AT1-7).

Angiotensinogen and Renin

RAS begins with the release of angiotensinogen into the bloodstream. Produced constantly in the liver, angiotensinogen is an inactive glycoprotein that, when cleaved, can directly originate Angiotensin I (Angio I) or Angiotensin II (Angio II). The replacement of estrogen in biological or synthetic form and glucocorticoids increase it liver production[10]. Some enzymes participate in the cleavage of Angiotensinogen, such as Tonin, Cathepsin G (both with increased function in inflammatory processes), and Renin. However, the role of the major protagonist in this process is that of renin[11].

Renin is an enzyme produced in the juxtaglomerular cells of the kidneys and its elevation occurs due to the signaling of decreased renal blood flow or by sympathetic stimulus[10]. Since RAS is one of the main blood pressure (BP) regulating systems in the medium (minutes) and long term (days, months), it is usually activated in the face of decreased BP. The low pressure in the renal afferent arterioles; the low blood flow in the dense macula of the distal renal tubules; and the sympathetic neural stimulus resulting from a fall in BP over the kidney's juxtaglomerular cells are all mechanisms that increase renin production. As the production of angiotensinogen by the liver is relatively constant, it is the production of renin that determines the increase in RAS activity[11]. It is important to understand that this is a BP regulatory system, therefore, it acts constantly, increasing or decreasing its vasoconstrictor and vasodilator activity through negative feedback.

The Role of Inflammation

Inflammation is a potent stimulus for the production of renin[12]. Studies indicate that inflammation increases the activation of the sympathetic autonomic nervous system, which, in turn, stimulates type 1 ß-adrenergic receptors in renal juxtaglomerular cells, increasing renin expression and the consequent RAS activity[10,12,13]. Therefore, any factor that stimulates inflammation, in effect, increases the activity of RAS.

Note that increased sympathetic autonomic discharge increases both renin production and inflammation itself. That is, therefore, a positive feedback mechanism, since greater production of renin leads to greater production of Angio II, which, in turn, when binding to AT1 receptors, can increase inflammatory activity in several tissues, including lungs, heart, and the sympathetic central nervous activity itself, which again favors renin production and inflammation. Furthermore, it is significant to report to the knowledge that in inflammatory, chronic or acute processes, not only renin but also other enzymes, tonin, and cathepsin G, previously mentioned, increase their activity favoring the transformation of angiotensinogen into Angio I and Angio II. Another factor that confirms the intensification of RAS in the face of inflammation[11].

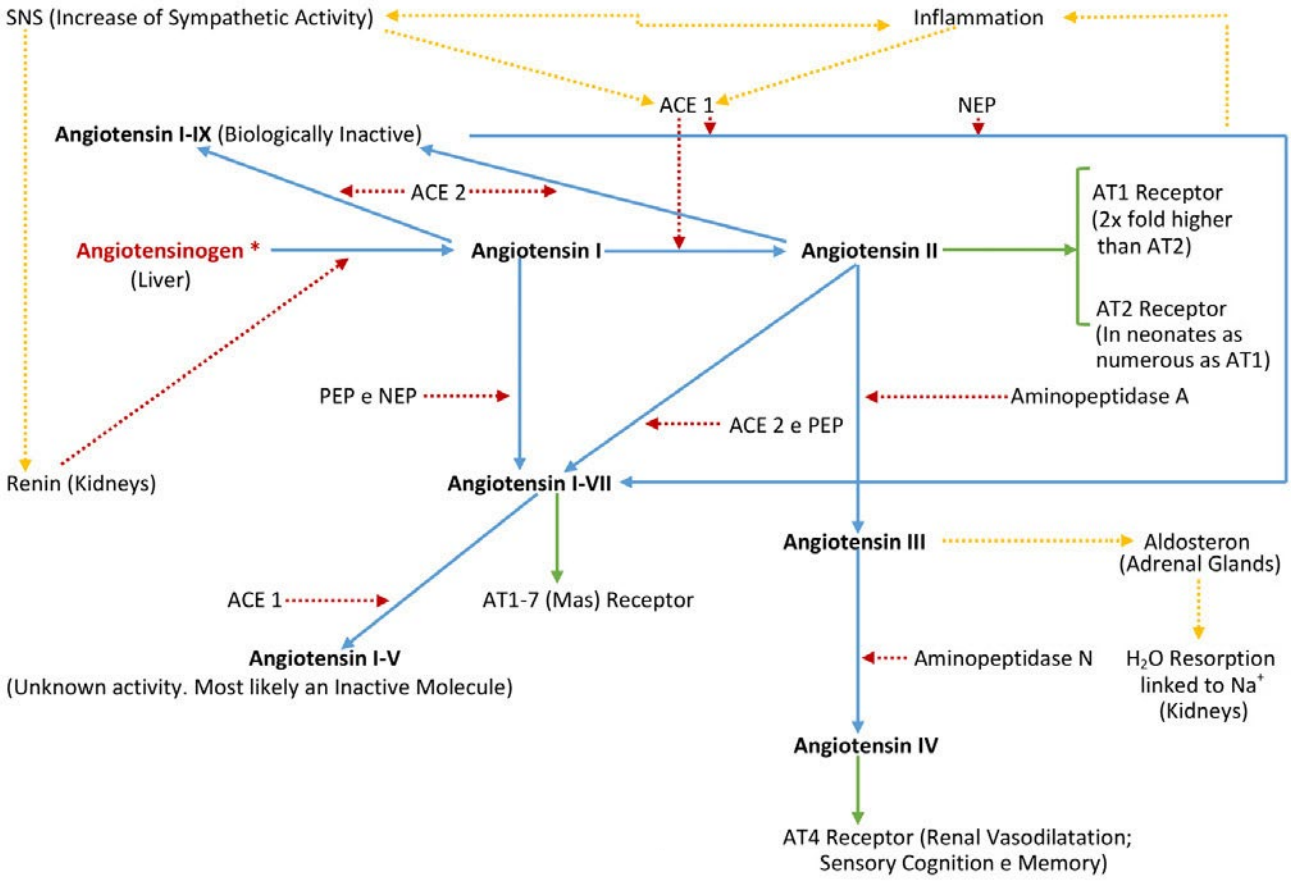
Angiotensin I, Angiotensin-Converting Enzyme 1 and Angiotensin I-VII

In the continuity of RAS, after the formation of Angio I, which is an essentially inactive molecule, its cleavage into Angio II by the action of ACE 1. ACE 1 is produced in the arterial vascular endothelium of all tissues, with greater production and the activity of this molecule in the pulmonary arterial vascular endothelium[9]. In addition to cleaving Angio I to form Angio II and cleaving Angio I-VII to form Angio I-V, ACE 1 participates in the breakdown of bradykinin into inactive compounds, BK (1-7).

Bradykinin is a potent vasodilator, bronchodilator, and natriuretic molecule, produced in the arterial vascular endothelium. Therefore, the increase in the production of ACE 1 favors the axis of BP rise controlled by the RAS, because, when binding to AT1 receptors, Angio II triggers direct vasoconstriction of arterial vessels and indirect via the production of vasopressin in the hypothalamus, in addition to inactivating a potent vasodilator – bradykinin[11].

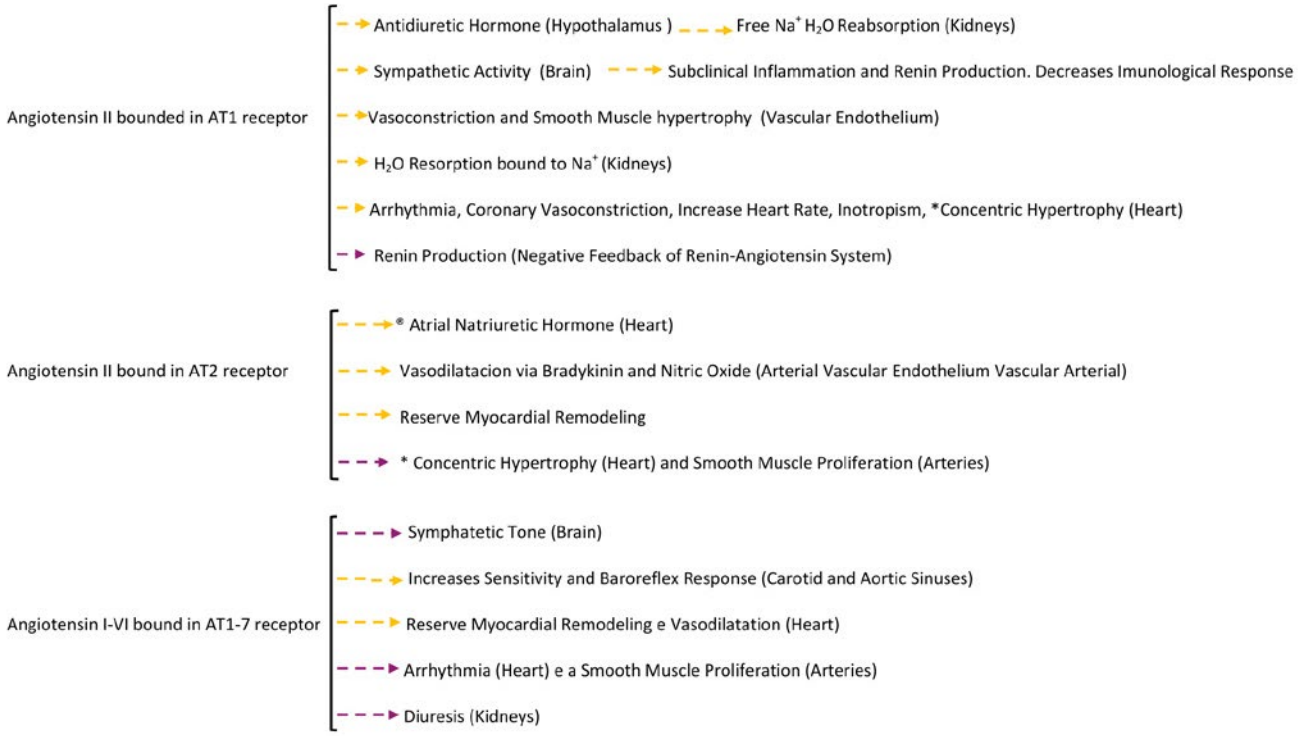
Angio I is an inactive molecule that besides being the precursor of Angio II is also a precursor of Angio I-VII and Angio I-IX. Prolil Endopepitase (PEP) and Neutral Endopeptidase (NEP) are the enzymes that act in the transformation reaction of Angio I into Angio I-VII and ACE 2 in that of Angio I into Angio I-IX. While Angio I-IX is a biologically inactive molecule, Angio I-VII triggers several important actions, most of which are contrary to Angio II, when it binds to AT1[9] receptors. Figure 1 shows that Angio I-VII can, through the action of ACE 1, transform into Angio I-V, a molecule previously recognized as inactive. Angio I-IX by the action of ACE 1 or NEP can become Angio I-VII. Figure 2 summarizes the actions of Angio I-VII when connecting to the receiver 1-7(Mas)[9].

Figure 1. Summary of interactions present in the renin-angiotensin system



Blue Solid Line – Indicates the direction of biochemical transformation. Green Solid Line – Indicates the binding of a molecule with its receptor. Red dashed line – Indicates the transformation by the enzyme. Orange dashed line – Indicates stimulus of production or elevation of the phenomenon. ACE 1 – Angiotensin Converting Enzyme (Somátic, produced in vascular endothelium, mainly in lungs). ACE 2 – Angiotensin Converting Enzyme (Germinal) (produced in epicardial endothelium and in intrarenal vessels intra-renais). PEP–prolil endopeptidase. NEP – Neutral endopeptidase. * – Start of Renin-Angiotensin System.

Figure 2. Mechanisms of action of angiotensins II and I-VI in different receptors



Orange dashed line – indicates the stimulus or increase of the phenomenon. Purple dashed line- Indicates inhibition of the phenomenon. ® Atrial natriuretic hormone – acts in kidneys. stimulate the natriuresis. * – Essential chronic effects.

One of the recent findings of the RAS is that Angio I-VII stimulates the expression and activity of cardiac SERCA 2, a protein located in the sarcoplasmic reticulum membrane that receives calcium into the terminal cistern, benefiting cardiac inotropism[14]. There are also the repercussions of Angio I-VII on the reproductive organs. In humans, the absence of the action of Angio I-VII is expressed in men, generating infertility, and in women, harming folliculogenesis and ovulation[10].

Angiotensin-Converting Enzyme 2

ACE 2, also called germinal ACE because it was first observed in testicular cells, has 42% of structural homology with ACE 1 (somatic). Although ACE 2 menseger ribonucleic acid (mRNA) is found in almost all body tissues, we know that it is produced mainly in the arterial endothelium of coronary arteries and intra-renal vessels, in pulmonary epithelial tissue and enterocytes. Also, it is produced by cardiac, renal, testicular, and smooth muscle cells[6]. The actions of ACE 2 are being increasingly unveiled by science. In a study conducted by Crackower et al.[15], it was found that the deletion of the gene that encodes ACE 2 in mice caused severe cardiac contractile dysfunction. We know that ACE 2 not only acts on Angio I but also acts on Angio II. ACE 2 and PEP can catalyze the reaction that cleaves Angio II to Angio I-VII. In addition, ACE 2 promotes the reaction that turns Angio II into Angio I-IX. It is also of great interest to highlight that ACE 1 inhibitors such as captopril and lisinopril, which are commonly used by hypertensive individuals, do not inhibit the action of ACE 2[16]. In this context, note that unlike ACE 1, ACE 2 benefits the RAS vasodilator balance, as it favors the transformation of Angio II (potentially vasoconstrictor and H2O retainer) into Angio I-VII (vasodilator).

The factors that lead to one or another reaction in the RAS are still not elucidated by the literature, but, under physiological conditions, this is a system that self-regulates to maintain acceptable BP levels. Depending on the body's needs, local neurohumoral or biochemical factors favor one or the other reaction. The transformation of Angio II into Angio I-VII favors vasodilation, decreased sympathetic tone and reverse myocardial remodeling.

On the other hand, when Angio II binds to AT1 receptors, it favors just the opposite - vasoconstriction, increased sympathetic tone and myocardial remodeling[9].

Angiotensin II, III and IV

Angio II is the central molecule of RAS. It is the most active among angiotensins and can follow five paths that lead to different effects, they are conversion to Angio I-VII; conversion to Angio I-IX; conversion to Angio III; connection to AT1 receptors; connection to AT2 receptors. As the conversions of Angio II into Angio I-VII and Angio I-IX have already been described, we will stick to the action of Angio III and the actions promoted by the connection of Angio II to its AT1 and AT2 receptors in this part of the text.

The conversion of Angio II to Angio III is mediated by the enzyme Aminopepitidase A. Angio III, in turn, can undergo another enzymatic action (Aminopeptidase N) and transform into Angio IV or bind to AT1 receptors, located in the adrenal glands and thus stimulate the production of Aldosterone. Aldosterone produced by the adrenals acts mainly on the kidneys, increasing the reabsorption of Na^+ bound to H_2O and elimination of K^+. This action favors the elevation of BP by increasing blood volume. It is important to report that there is still no consistent evidence on the existence of a specific AT3 receptor for Angio III[9].

Angio IV binds to AT4 receptors located mainly in the renal arteries and brain and is also found, to a lesser extent, in the heart, the smooth muscle of the arterial blood vessels, and adrenal glands[17]. Angio IV, when it binds to its AT4 receptor, promotes renal arterial vasodilation and stimulates the fixation of memory and sensory and motor cognition, by stimulating the production of Dopamine in the striated ganglia of the brain[9]. It is noteworthy that the cerebral distribution of receptors AT4 is distinct from that of AT1 and AT2 receptors. The effect of Angio IV on the central nervous system is reinforced by research that caused AT4 receptor inhibition, observing the loss of spatial memory in rats[9]. Such studies indicate that Angio IV inhibition may be linked to Alzheimer's, seizures, and Parkinson's disease[9]. Research on Angio IV has grown, both from its action on the central nervous system and from its tissue action. Possibly, in the coming years, interesting news will emerge, such as that Angio IV can bind to AT1 receptors in blood vessels and cause arterial vasoconstriction[18]. Findings like this demonstrate the complexity of the RAS and the multifaceted relationship between its components.

Angiotensin II and AT1 and AT2 Receptors

The main actions of Angio II when binding to the AT1 and AT2 receptors are summarized in Figure 2. The largest volume of publications on the RAS is precisely on the effects of Angio II when binding to the AT1 receptor, corresponding to 60% of the publications on the subject[9]. In adult rats, there is a predominance of approximately 1.9 AT1 receptors for each AT2 receptor, as observed in cardiac cells in the study by Tadevosyan et al.[19].

The AT1 and AT2 receptors are found in virtually all body tissues. However, we know that there are two AT1 receptor subtypes (AT1a and AT1b), with 95% sequential amino acid homology being functionally identical. The AT1a receptor is mainly expressed in the heart, brain, and blood vessels, whereas AT1b has a limited localization to endocrine tissues, such as the adrenal and pituitary glands[20].

Of all the actions of the systemic RAS, those that have implications for the cardiovascular system are the ones that draw the most attention. The local (tissue) production of all RAS elements in the heart, from the formation of angiotensinogen to inactive molecules such as Angio I-IX, and the discovery of AT1 and AT2 receptors in the cardiac cell's nuclear membrane, denote the importance of this system for heart functions[18]. For example, the discovery of these receptors on the nuclear membrane raises the mechanistic hypothesis that Angio II, when bound to AT1 receptors, can induce changes in the transcription of cardiac genes, indicating that Angio II acts through intracellular receptors to regulate the growth of cardiomyocytes and induce cardiac hypertrophy.

Corroborating this idea, Reudelhuber et al.[21] point out that the increased expression of AT1 is a more potent stimulus to myocardial remodeling than the marked elevation of Angio II, suggesting that the density of AT1 may be the limiting factor for hypertrophy caused by Angio II. Cardiac hypertrophy, mediated by systemic and tissue RAS, is essential to balance the maintenance of cardiac mass in the face of various physiological and pathological actors, extrinsic and

intrinsic, such as physical exercise, cardiac cachexia, and SAH.

Thinking about the pathological spectrum, the chronic activation of the AT1 receptor by Angio II favors the onset of SAH, cardiac arrhythmias, stroke, the proliferation of intramyocardial fibroblasts, and metabolic disorders, such as Diabetes Mellitus and Dyslipidemia[20]. In the physiological aspect, the production of tissue Angio II by cardiomyocytes, due to the increase in cardiac preload during physical exercise, increases myocardial contractility, which is important for the increase in cardiac inotropism in moderate to high-intensity efforts[22].

The actions of Angio II are essential to the conservation of the basic function of the cardiovascular system, which is body homeostasis through the adequate maintenance of blood flow to the various body tissues, at rest or physical effort. The disease state is caused by the imbalance of the actions of Angio II when it binds to the AT1 receptors. This imbalance is caused by several factors, including inflammation arising, for example, from metabolic changes (Diabetes Mellitus, dyslipidemia, and obesity), vascular changes (SAH), and smoking[20].

Note another interesting point, the positive feedback of inflammation in diabetics. Patients with RAS homeostasis imbalance have decreased insulin sensitivity. Studies in rats have shown that activation of the AT1 receptor by Angio II hinders insulin signaling, triggering insulin resistance in the medium and long term[23]. Normally, the binding of insulin to its receptor phosphorylates tyrosine and activates phosphatidylinositol-3 kinase (PI3K). In human umbilical vein endothelial cells, Angio II impaired the coupling of insulin to its receptor and also increased the phosphorylation of serine, a mechanism that, in skeletal muscle cells, interferes with insulin signaling and the consequent translocation of Glut4 from the cytosol to the membrane[24]. Therefore, the RAS imbalance can induce Diabetes Mellitus, which, in turn, increases inflammation and feeds the RAS activity, positive feedback from an effectively pathogenic cycle.

In the central nervous system, the binding of Angio II to AT1 receptors stimulates, in the magnocellular neurons of the hypothalamus, the production of vasopressin (antidiuretic hormone), which generates arterial vasoconstriction by binding to receptors in the arterial vascular endothelium and the reabsorption of free H_2O sodium by the distal renal tubules. Both effects favor the balance of BP elevation. Also, in the central nervous system, Angio II increases the sympathetic autonomic tone when interacting with AT1, increasing the release of catecholamines, especially noradrenaline, through peripheral nerve endings[25], a mechanism that favors the appearance of arrhythmias.

In the adrenal glands, Angio II stimulates the production of catecholamines, adrenaline, and norepinephrine. Specifically, the high adrenaline production stimulates the acute and chronic increase in BP, since adrenaline, when it binds to endothelial α-adrenergic receptors in the arteries, strongly favors vasoconstriction. This mechanism is often observed in patients with chronic SAH[26].

Finally, it is imperative to address the role of Angio II in carcinogenesis. Cell proliferation and angiogenesis regulated by the AT1 receptor have powerful implications for cancerous tumors. The tissue production of Angio II is a pro-angiogenic stimulus in the tumor microenvironment. Tumors implanted in mice developed intensive angiogenesis with the induction of vascular endothelial growth factor (VEGF) in the tumor stroma. The production of angiogenic factors, induced by Angio II, involves the signaling pathway of the AT1 receptor. Therefore, the use of inhibitors of AT1 receptors as drugs that block AT1 can be an effective therapy against tumor growth[27]. It is also known that Angio II plays a role in the growth and chemoresistance of pancreatic cancer cells, positive for AT1 receptors, due to its action as a potent mitogenic and anti-apoptotic molecule[9]. Furthermore, the action of Angio II on several other types of cancer has been reported, such as liver, breast, and prostate carcinoma[9].

The physiological role of the AT2 receptor is at least controversial. Expressed mainly in fetal tissues, it reduces its presence in tissues with advancing age. In adults, it is restricted to some organs, such as kidneys, brain, heart, adipose tissue, adrenal cells, skin, myometrium, and ovary[8]. AT2 receptors are re-expressed during situations such as cardiac and vascular injury (myocardial infarction, left ventricular concentric hypertrophy, and vascular proliferation of smooth muscle), in peripheral nerve injuries, and chronic sodium depletion. The knowledge of the high expression of this receptor in intrauterine life and its re-expression in adults who suffer tissue damage suggest a strong weighting effect on tissue structuring and restructuring[9]. Corroborating this idea, the polymorphism of the gene encoding AT2 causes congenital anomalies of the urinary tract in humans, reinforcing its importance in the development of organs and systems such as the urinary[28].

Despite all these beneficial effects, the expression of AT2 receptors and their interaction with Angio II is associated with situations, such as concentric hypertrophy and apoptosis of cardiomyocytes, apoptosis of pancreatic cells, adipose and neural tissue, for example, in the hypothalamic region[9]. There is also evidence that AT2 receptors mediate nociceptive pain. Drugs that inhibit neural AT2 receptors are being studied to reduce nociceptive pain[29]. The controversial actions of Angio II, when interacting with AT2 receptors, will still show developments that will possibly resonate, in science and clinical practice, in a striking way in the coming years.

Figures 1 and 2 summarize the RAS and the main physiological implications triggered by active angiotensins. For better visualization, in Figure 1, angiotensins are highlighted in bold, and angiotensinogen (considered the beginning of RAS) is highlighted in red.

Interaction between the Renin-Angiotensin System and SARS-CoV-2

As stated earlier, the functional receptor for SARS-CoV-2 is ACE 2. Although it is known that ACE 2 mRNA is present in virtually all organs, its expression was initially described in the arterial endothelium of coronary arteries and intra-renal vessels, is also produced locally by cardiac, renal, testicular, and smooth muscle cells[6]. However, an important study by Hamming et al.[30], in which 93 individuals were evaluated, identified a large superficial expression of ACE 2 in pulmonary alveolar epithelial cells (especially Type II) and small intestine enterocytes. The authors demonstrated that ACE 2 is expressed superficially and abundantly in humans, in the epithelia of the lung and small intestine, which may provide potential routes of entry for SARS-CoV and currently for SARS-CoV-2, since these cells maintain direct contact with the external environment. That explains why the main form of contagion is through droplets of saliva dispersed in the air that can enter the respiratory airways, and also through the contaminated hand in contact with the nostrils[30]. We could ask ourselves: why are there no reports of oral contagion if the presence of ACE 2 is abundant in the intestine? The hypothesis is that the acidic pH of the digestive system disables the viral action.

Initial viral entry can cause cytopathological changes at the alveolar-capillary interface. In SARS-CoV-2, the abundant expression of ACE 2 in type II alveolar cells, responsible for the surfactant production that prevents alveolar collapse, provides a fast base for viral expansion and a vicious circle of diffuse and progressive alveolar wall destruction. This mechanism explains why individuals with lung diseases infected with SARS-CoV-2 have greater clinical complications and mortality.

In this context, a curious aspect is smoking. There is a pathophysiological rationale that leads us to think about a strong association between smoking and SARS-CoV-2. In SARS-CoV-2, the change in protein S has an affinity 10 to 20 times greater for ACE 2 than in SARS-CoV-2[34]. As cigarette smoke increases the expression of ACE 2 in type 2 pneumocytes and alveolar macrophages[35], it is plausible to imagine that smokers are more likely to be infected and to have more advanced stages of the disease. However, the works published so far do not ratify this association. In the study by Guo et al.[31], only 10% of the individuals evaluated who developed stage IV or progressed to death (stage V) were smokers. In the study by Wu and McGoogan[32], it was reported that 50% of men, but only 3% of women, who had more advanced stages of the disease (IV and V) were smokers. Still in this line of thought, Zhang et al.[33], in a survey of 140 people who were hospitalized for greater severity of the disease, identified that only 6.4% of patients were smokers.

Therefore, although some scientists point out that smoking facilitates viral load mediated by ACE 2[36], the data presented here leaves us in doubt whether smoking is an aggravating factor for SARS-CoV-2.

The spectral characteristic of SARS-CoV-2 does not depend only on the concentration of ACE 2 in the respiratory airways and on the respiratory condition of the infected individual. Another fact to note is that SARS-CoV-2, when it binds to ACE 2 through its protein domain S (Spike) to replicate and have access to body cells, inactivates ACE 2. As already explained in this article, the activity of ACE 2 in the RAS favors the balance of BP reduction by acting on the transformation of Angio I into Angio I-IX and Angio II into Angio I-IX or Angio I-VII. Imai et al.[36] conducted a study in which acute lung injury was induced by acid aspiration in rats with and without ACE 2 deletion. As a result, the authors observed that rats with ACE 2 deletion, in addition to massive pulmonary edema, showed a 14% increase in pulmonary capillary vascular permeability, an increase of 26% in inflammatory cell infiltration, a 33% decrease in hematosis, and an approximately 52% increase in the concentration of Angio II in the lungs, compared to rats with acute lung injury, but without ACE 2 deletion. Acute lung injury caused by infectious processes increases lung elastance, hampering ventilatory mechanics and hematosis. In rats in which acute lung injury was induced without ACE 2 deletion, lung elastance increased by 90% compared to the control group without pulmonary injury, while in rats with acute respiratory injury and ACE 2 deletion the increase was 200% in comparison to control. Thus, the authors concluded that acute lung injury results in decreased expression of ACE 2 and that, unlike ACE 2, ACE 1 favors the pathogenesis of the disease by increasing the production of Angio II.

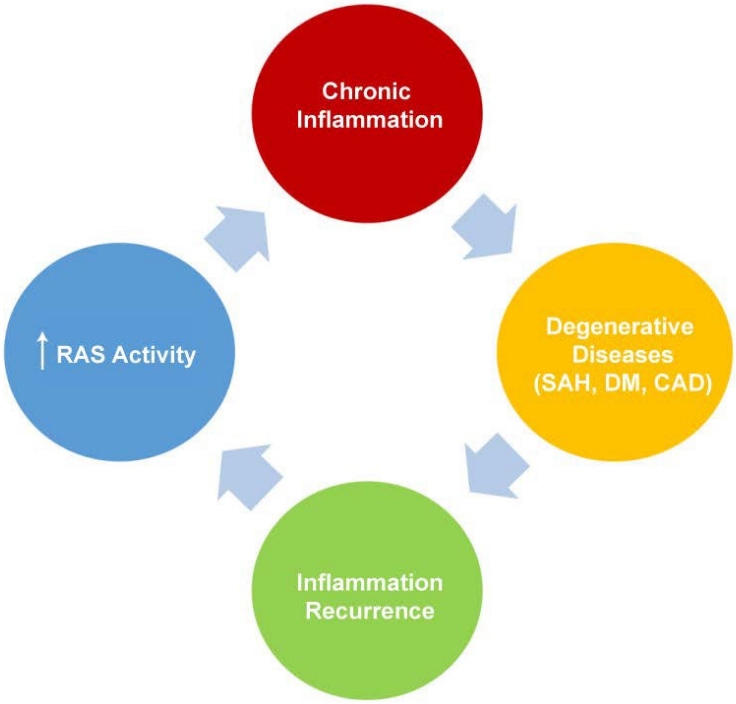
It is clear that the lung injury caused by SARS-CoV-2, associated with the inactivation of ACE 2 and the consequent increase in the ACE 1 activity, increases the concentration of Angio II and triggers positive feedback of all pathogenesis caused by the infection. Furthermore, under normal conditions, 80% of the bradykinin produced by the arterial vascular endothelium is inactivated in the lungs by ACE 1. In the condition caused by SARS-CoV-2, the inactivation of bradykinin may be even greater, which favors bronchoconstriction and worsens the clinical condition.

Still, in this perspective, the lungs express the AT1a and AT2 receptors. Inactivation of ACE 2 increases the stimulation of AT1a receptors, which, when interacting with Angio II, leads to lung injury[36]. Given this explanation, it is plausible to think that drugs such as AT1 receptor antagonists, as well as ACE 1 inhibitors, could benefit patients with SARS-CoV-2, however, no study reported benefits or harms of the use of these drugs[37]. In summary, we hypothesized that by inactivating ACE 2, SARS-CoV-2 stimulates the greater activity and expression of ACE 1, AT1a, and Angio II receptors, molecules of the RAS that favor the evolution of the disease and worsen the prognosis of infected patients. It is worth mentioning that such questions can be elucidated by the Randomized Clinical Trial being developed by the University of Minnesota (ClinicalTrials.gov number, NCT04287686.). The study intends to investigate the effects of losartan on SARS-CoV-2 therapy developed by two groups of patients who had previously received treatment with RAAS inhibitors and are hospitalized (NCT04312009.) Or not (NCT04311177.)[38].

At this point, we cannot doubt the role of inflammation in this interaction between SARS-CoV-2 and RAS. As previously mentioned, inflammation is one of the substrates that positive feedback the RAS, for example, causing dysfunction of the arterial vascular endothelial wall, increasing the activity of the main elements of the balance favorable to the elevation of BP[9,11]. At the same time, the viral infection that triggers tissue damage feeds the inflammatory process and thus creates a fertile ground for its spread. Nevertheless, individuals who have favorable conditions for inflammation are more susceptible to the installation of SARS-CoV-2. It is perhaps not coincidental that people with SAH (32%), Diabetes Mellitus (15%) and Coronary Artery Disease (11%) are those who present the most aggressive disease, representing 73% of those who progress to death[31]. Hypertensive, diabetic or coronary disease individuals are those who frequently exhibit increased inflammatory markers and, consequently, feed the cycle Illness RAS Illness, with inflammation as a subsidy of feedback[39,40].

Corroborating this idea, the study by Guo et al.[31] demonstrated a high positive linear correlation between C-reactive protein and levels of N-terminal pro-cerebral natriuretic peptide (NT-proBNP), an important marker of cardiac dysfunction and injury. Add to this cycle the knowledge that inflammation decreases the immune reserve[41] and we will then have all the subsidies for the installation and the aggressiveness of SARS-CoV-2. Figure 3 schematically represents this cycle.

Figure 3. Inflammation, Illness, Renin-Angiotensin System (RAS) cycle. SARS-CoV-2 benefits from this cycle in patients with Systemic Arterial Hypertension (SAH), Diabetes Mellitus (DM) and Coronary Artery Disease (CAD) to settle and spread in the host's body. This is one of the mechanisms that explains the aggressiveness of SARS-CoV-2



The high prevalence of previous cardiac diseases in people who die in SARS-CoV-2 possibly has another association with RAS. The presence of a complete RAS in cardiac cells and coronary vessels seems to be an extremely fertile field for the performance of SARS-CoV-2. It is possible that, although this has not been suggested in any mechanistic study of the disease, the virus easily penetrates the cardiac tissue and coronary artery vessels due to the abundant presence of ACE 2. Once inside the cardiac cell, SARS- CoV- 2 causes inactivation of ACE 2, which, consequently, favors the expression and activity of Angio II, ACE 1 and AT1 receptors, with a consequent decrease in the production of Angio I-VII and the activity of AT1-7 and AT2 receptors. Together, this RAS imbalance promotes the onset of arrhythmias such as tachycardia and ventricular fibrillation, myocarditis due to intense inflammatory activity associated with myocardial injury, with a consequent decrease in systolic function and proliferation of intramyocardial fibroblasts, a situation reported in several studies[31-33]. As the outcome of the TRED-HF study with asymptomatic patients and patients with heart failure with recovered left ventricular ejection fraction, suspension of medication doses (including RAAS inhibitors) resulted in new episodes of dilated heart disease[42].

Still, many infected patients who died had myocardial infarction caused by coronary spasm or by increased coronary endothelial thrombogenic activity and/or destabilization of the pre-existing atherosclerotic plaque[31,43]. Revisiting the RAS explained in this article, it is clarifying the understanding of why this happens. As previously described, the RAS imbalance with decreased production of Angio I-VII and a consequent increase in Angio II production favors the pro-thrombogenic and inflammatory balance[11,14,18,20-23,25,28], which explains the outcome of myocardial infarction in patients who progressed to SARS-CoV-2 stages IV and V.

We also raised another hypothesis, that the RAS tissue production dictates which are the main target organs of SARS-CoV-2. It is reinforced by another finding in the articles that describe the characteristics of patients who have been contaminated and hospitalized. In the study by Guo et al.[31], only 3% of the 187 patients studied initially had kidney disease, and during the hospitalization period, 14% developed kidney disease. However, the predominance is higher among critically ill patients[44].

As already mentioned, the kidneys also exhibit complete local RAS production. The presence of kidney disease does not seem to favor the installation of SARS-CoV-2 but appears as a result of it. In the kidneys, the decrease in the ACE 2 activity in the renal arteries can cause vasoconstriction and reduced flow in the afferent arterioles, leading to increased production of renin and consequently the entire systemic RAS.

However, even in the face of all this contextualization of the interaction between SARS-CoV-2 and RAS, the multifaceted characteristic of SARS-CoV-2 generates questions that are currently unanswered, such as how much acute liver impairment due to viral infection feedback positively the RAS and SARS-CoV-2 itself, as also reported in the study by Guo et al.[31] The lack of surveys on the previous presence of obstructive sleep apnea/hypopnea syndrome in the most severe patients may be an undervalued characteristic of patients with SARS-CoV-2 since it is strongly associated with SAH, cardiovascular diseases, the elevation of RAS activity, and inflammation. More specifically, we know that there is a significant amount of AT1 receptors in the carotid sinus. The greater endothelial production of Angio II induces an increase in the activity of peripheral chemoreceptors located in this region. As a consequence, there is an increase in sympathetic activity and a consequent increase in inflammation, cardiac work (increased heart rate and myocardial contractility), ventilation, and total peripheral resistance (vasoconstriction). The awakening of this cascade begins with intermittent hypoxia arising from the apnea/hypopnea syndrome during sleep[45]. Therefore, it seems very logical to us that people with this syndrome have worse clinical evolution when infected. However, this has been little explored in the literature.

Another point, why are there no reports of individuals with acquired immune deficiency syndrome infected with SARS-CoV-2, since this disease drastically affects the immune defense and is the cause of high chronic inflammation? Possibly future studies will help us to answer these questions and to better understand the interaction between SARS-CoV-2 and RAS.

Conclusion

Based on the mechanistic studies and clinical description of SARS-CoV-2, it is possible to trace strong and diverse interactions between the renin-angiotensin system and SARS-CoV-2. However, the elucidation of these interactions still does not provide all the answers to the questions and findings that permeate this pandemic. The spectral characteristic of SARS-CoV-2 and its interaction with the renin angiotensin system will still be a plentiful ground for future scientific investigations.

Author contributions

Petto J participated in the conception, design, search, interpretation of results and writing of the scientific article. Santos PHS participated in the search, interpretation of results and writing of the scientific article. Santos LFS and Sena DSS participated in the search and writing of the scientific article. Sacramento MS participated in the search, interpretation of results and writing of the scientific article.

Competing interests

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to, grants and funding, participation in advisory council, study design, preparation of the manuscript, statistical analysis, etc.).

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