Renin-angiotensin-aldosterone system inhibitors and covid-19 complications

Inibidores do sistema renina-angiotensina-aldosterona e complicações da covid-19

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ABSTRACT

The world faces today a pandemic of unquestionable importance, caused by an infection with a new enveloped RNA virus that belongs to the Coronaviridae family. The new coronavirus (SARS-CoV 2) uses a glycoprotein present on its surface to bind to and infect host cells that express the angiotensin converting enzyme II (ACE-2). Although different tissues may be targeted by the virus, respiratory complications remain as the main cause of death. It has been demonstrated that Renin-Angiotensin-Aldosterone System (RAAS) inhibitors increase ACE-2 expression in animal models, raising the concern that patients under treatment with these drugs could become more susceptible to COVID-19 complications. Here, we discuss the impact of RAAS inhibitors on COVID-19 outcomes and show that no evidence so far supports that the use of these drugs could pose a risk to SARS-CoV 2-infected patients. In fact, clinical data suggest that RAAS inhibitors may even act in a protective way against COVID-19 complications and should not be discontinued.

Keywords: SARS-CoV 2, Antihypertensives, Renin-Angiotensin-Aldosterone System inhibitors, ACE-2. COVID-19.

RESUMO
O mundo enfrenta, atualmente, uma pandemia de importância inquestionável, causada por uma infecção com um novo vírus de RNA envelopado, que pertence à família Coronaviridae. O novo coronavírus (SARS-CoV 2) utiliza uma glicoproteína presente em sua superfície para se ligar e infectar células hospedeiras que expressam a enzima conversora da angiotensina II (ECA-2). Embora diferentes tecidos possam ser infectados pelo vírus, as complicações respiratórias continuam sendo a principal causa de morte. Foi demonstrado que os inibidores do Sistema Renina-Angiotensina-Aldosterona (SRAA) aumentam a expressão de ECA-2 em modelos animais, levantando a preocupação de que os pacientes em tratamento com estes medicamentos poderiam se tornar mais suscetíveis às complicações da COVID-19. Aqui, discutimos o impacto dos inibidores do SRAA no prognóstico da COVID-19 e demonstramos que, até o presente momento, nenhuma evidência apoia que o uso destes medicamentos possa representar um risco para os infectados com o SARS-CoV 2. Na verdade, os dados clínicos sugerem que os inibidores do SRAA poderiam até mesmo atuar de forma protetora contra as complicações da COVID-19 e não devem ser descontinuados.

Palavras-chave: SARS-CoV 2, Anti-hipertensivos, Inibidores do Sistema Renina-Angiotensina-Aldosterona, ECA-2, COVID-19.

1 INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) is an enveloped RNA virus of the Coronaviridae family (1, 2). This family is composed by a few different types of coronaviruses, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). So far, seven viruses of this family have been described to be capable of causing humans diseases (3, 4). The Coronaviridae family is divided into two subfamilies: the Letovirinae subfamily and Orthocoronavirinae subfamily (5). The Orthocoronavirinae subfamily is further divided into four genera: alpha, beta, gamma, and delta coronavirus (5). Along with SARS-CoV and MERS-CoV, SARS-CoV 2 has also been classified as a beta coronavirus (1, 6).

SARS-CoV 2 infection is the cause of Coronavirus disease 2019 (COVID-19), characterized by persistent cough, fever, loss of appetite, fatigue, abdominal pain, diarrhea and, in more severe cases, intense dyspnea. Hyposmia and hypogeusia have also been identified in several patients (7, 8). Coronaviruses receive this name due to the presence of spikes on its surface that create an aspect similar to a crown (9). The binding of spike glycoproteins to angiotensin-converting enzyme II (ACE-2) present on the

surface of host cells promotes infection of different tissues, especially the respiratory epithelium (10).

Antihypertensive drugs like angiotensin receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibitors have been clinically used to control blood pressure levels and, by reasons that are not yet fully understood, shown to promote increased expression of ACE-2 in animal models (11-14). Therefore, the clinical impact of these drugs on SARS-CoV 2-infected patients has been object of raising concern and will be discussed in this review.

2 SARS-COV 2 - CELL ENTRY MECHANISM

The SARS-CoV 2 S gene encodes an extremely important protein for its infectious capacity, called Spike or S protein (15). The structure of the S protein is characterized by two subunits: subunit 1 (S1) and subunit 2 (S2) (16, 17). S1 has a receptor biding domain (RBD), which has high affinity to interact and bind to ACE-2, allowing the virus to attach to the cell, while the S2 subunit is responsible for the fusion between the SARS-CoV 2 membrane and the host cell membrane (10, 16). The interaction between S protein and ACE-2 is the same that occurs between SARS-CoV and human cells (16). Despite having very similar infectious mechanisms, SARS-CoV 2 has a RBD with greater affinity for ACE-2 when compared to SARS-CoV (16). In addition, the transmembrane serine protease 2 (TMPRSS2) present on the surface of host cells has also been suggested as important for SARS-CoV 2 infection mechanism, being responsible for cleaving S protein in the division between subunit 1 and subunit 2 or cleaving the S protein directly in subunit 2, resulting in its activation (18, 19).

3 ANTIHYPERTENSIVE DRUGS AND ACE-2

The Renin-Angiotensin-Aldosterone System (RAAS) plays a crucial role in the physiological maintenance of blood pressure. The liver is responsible for producing and releasing angiotensinogen into the bloodstream; at times when there is a decrease in the blood pressure in the afferent arterioles, juxtaglomerular cells release renin, which is responsible for transforming the angiotensinogen into angiotensin I; then, angiotensin I is transformed into angiotensin II due to the action of the angiotensin converting enzyme, a process that mainly occurs in the lungs. When binding to AT1 receptors in blood vessels and adrenal glands, angiotensin II leads to vasoconstriction and aldosterone-mediated

increase in reabsorption of sodium and water, culminating in higher blood volume and pressure (20).

In 2000, a new component of RAAS was discovered and given the name angiotensin converting enzyme II (21). ACE-2 is a monocarboxypeptidase, which has the ability to remove a leucine amino acid from angiotensin I to form the angiotensin (1-9) peptide, which is further cleaved to form angiotensin (1-7), a peptide that counteracts angiotensin II, mediating vasodilatation (21). Alternatively, ACE-2 directly metabolize angiotensin II through the cleavage of a terminal phenylalanine amino acid, forming angiotensin (1-7) (22).

Several classes of antihypertensive drugs have been developed based on RAAS and are widely used in the clinics. Angiotensin receptor blockers prevent the binding of angiotensin II to the AT1 receptor, while ACE inhibitors are able to inhibit the angiotensin-converting enzyme; both mechanisms resulting in decreased blood pressure. The use of these antihypertensive drugs, however, has been associated to ACE-2 overexpression in animal models (11-14).

Ferrario *et al*. administered placebo, losartan (an ARB) and lisinopril (an ACE inhibitor), or the drug combination to rats and observed that animals receiving only losartan presented increased angiotensin II and angiotensin (1-7) plasma levels, and higher cardiac expression and activity of ACE-2 (23). Although animals receiving only lisinopril had increased plasma levels of angiotensin (1-7) and ACE-2 gene expression in cardiac tissue, plasma levels of angiotensin II were decreased and there was no impact on ACE-2 activity (23). The drug combination was shown to promote high activity of ACE-2 in the cardiac tissue (23). Wang *et al*. analyzed the effects of different ARBs on RAAS components, demonstrating that the expression of both ACE-2 and angiotensin (1-7) was higher than normal (12). Ishiyama *et al*. evaluated the impact of losartan and olmesartan on rats during 28 days after coronary artery ligation and found that ACE-2 mRNA expression was increased after administration of these drugs (14). Urinary level of ACE-2 was found to be higher among patients who were under treatment with olmesartan (ARB), suggesting that some RAAS inhibitors may have a positive impact on ACE-2 expression in human subjects (24).

Given the well-stablished SARS-CoV 2 ability to interact with ACE-2 on host cells and data demonstrating ACE-2 overexpression after the use of RAAS inhibitory drugs, one could hypothesize that patients under chronic use of these medications could have increased susceptibility to the complications of COVID-19 (11, 25, 26). Here, we

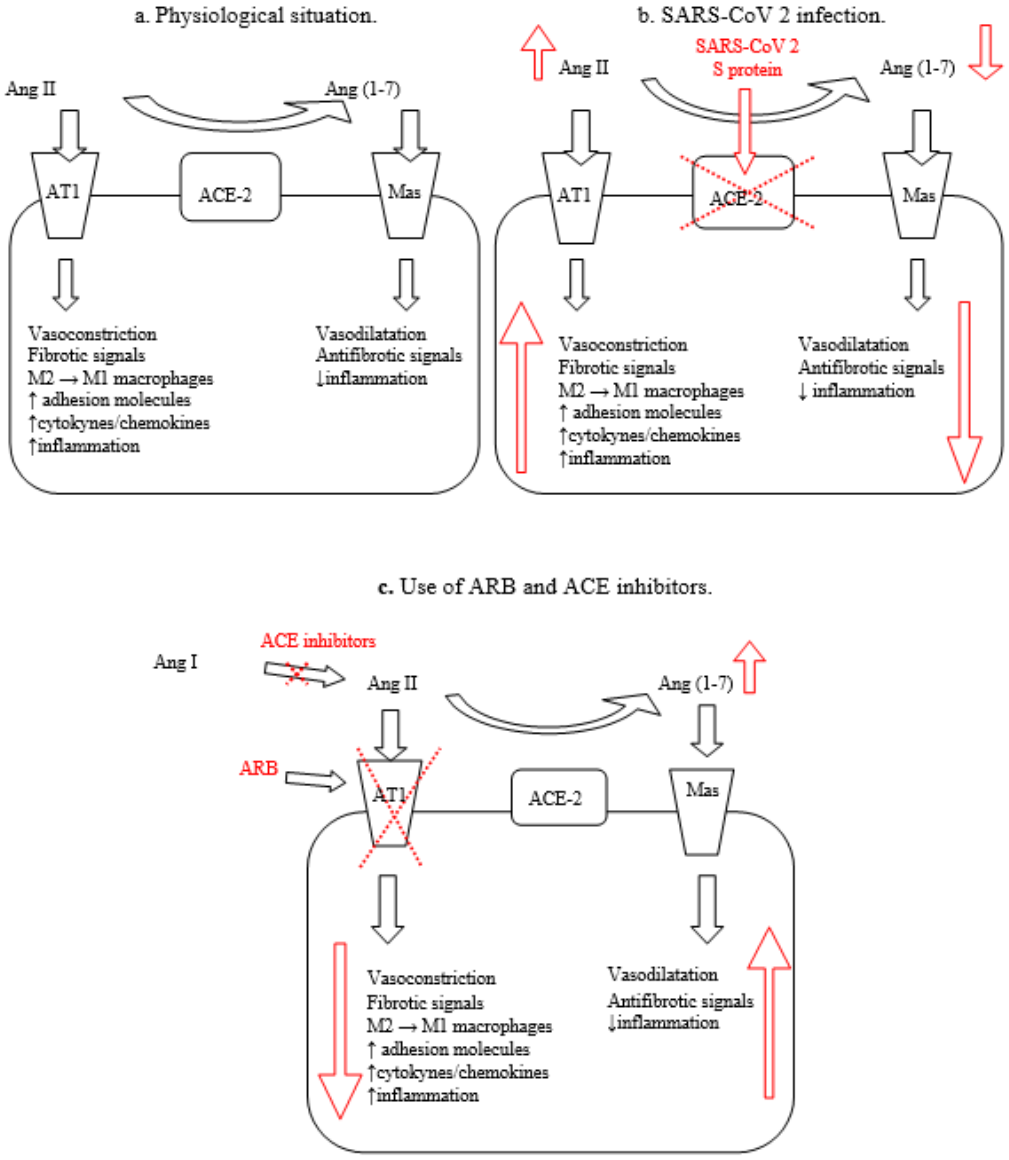
discuss recent clinical data on this subject in order to contribute to a better understanding of the risks threating hypertensive patients in the context of the COVID-19 pandemic.

4 ACE-2, INFLAMMATION AND LUNG DAMAGE

In physiological circumstances, the action of Renin-Angiotensin-Aldosterone System remains in a state of dynamic equilibrium, therefore, there is no harm to the organism (Fig. 1A) (27). However, in some pathological situations, such as the presence of SARS-CoV 2, ACE-2 activity could be downregulated due to its interaction with the S protein (28, 29), leading to a lower production of angiotensin (1-7) and accumulation of angiotensin II, which causes exacerbation of proinflammatory and fibrotic signals mediated by the ACE / Ang II / AT1 axis, resulting in lung damage (Figure 1B) (29).

When angiotensin II activates the AT1 receptor, it causes an upregulation in the expression of some adhesion molecules, such as E-selectin, P-selectin, intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), leading to increased numbers of inflammatory cells migrating from blood to tissues, which contributes to the inflammatory process (30, 31). Moreover, angiotensin II has the ability to induce polarization of macrophages into M1 phenotype, which produces large amounts of proinflammatory cytokines, such as TNF-α, IL-6 and IL-1, contributing to a greater inflammatory process and tissue damage (30, 32). Also, angiotensin II, acting through its AT1 receptor, is able to stimulate cytoskeletal rearrangements in T cells and can also stimulate the release of some specific cytokines and chemokines, culminating in recruitment of T cells to inflammation sites (33). A further boost to inflammation could also be expected as lower activation of the ACE-2 / Ang (1-7) / Mas axis may result in less anti-inflammatory signals, contributing to inflammation and tissue damage (34). In addition, lower production of angiotensin (1-7) may also have a negative impact on protective and antifibrotic signals induced by the ACE-2 / Ang (1-7) / Mas axis (Fig 1B) (29). Therefore, it is possible that inhibiting the ACE / Ang II / AT1 axis with these antihypertensive drugs could lead to a decrease in proinflammatory signs and lung damage, protecting patients from worst prognosis (Figure 1C) (27).

Figure 1.



4.1 RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM IN THE CONTEXT OF SARS-COV 2 AND ANTIHYPERTENSIVE DRUGS.

The Renin-Angiotensin-Aldosterone System works in balance under physiological conditions **(a)**. SARS-CoV 2 infection interferes with ACE-2 activity, leading to Ang II accumulation, enhanced pro inflammatory and fibrotic signals, and decreased Ang (1-7) concentration, culminating in inflammation and lung damage **(b)**. ARB and ACE inhibitors may act in a protective way against inflammation and fibrosis, inhibiting the ACE- Ang II/ AT1 axis and indirectly stimulating the ACE-2/ Ang (1-7)/ Mas axis, leading to increased anti-inflammatory and antifibrotic signals, which could result in lower lung damage **(c)**.

5 HYPERTENSION AND COVID-19

Hypertensive patients have a higher risk of developing severe COVID-19 symptoms (35, 36). Huang *et al.* analyzed outcomes of 310 patients diagnosed with COVID-19 and concluded that hypertensive individuals had a higher mortality rate compared to non-hypertensive individuals, in addition to also being more likely to develop the severe form of COVID-19. It was observed a higher number of hypertensive patients who required ICU admission and mechanical ventilation when compared to non-hypertensive individuals (37). Also, hematological analysis showed that COVID-19 hypertensive patients had higher levels of neutrophils, lymphocytes and fibrinogen when compared to non-hypertensive ones, indicating that, in these individuals, the inflammatory response and, consequently, the damage to tissues and organs could be more intense (37).

The severity of COVID-19 occurs not only due to the pathological actions of SARS-CoV 2 in the body, but also due to the excessive immune response of the host, with release of cytokines, such as TNF, IL-1 and IL-6, causing a cytokine storm and also symptoms of sepsis, which represents 28% of all COVID-19 fatal cases (38). Therefore, it is possible that the stronger inflammatory response seen in hypertensive patients with COVID-19 could be one of the explanations for the relationship between hypertension and a greater susceptibility to severe symptoms of the disease. Another possible explanation for why hypertensive individuals have higher morbidity and mortality have emerged, as the use of ARBs and ACE inhibitors, were shown to increase the expression of ACE-2 (11). However, as it is summarized in table 1 and discussed below, clinical data have surprisingly contradicted the later hypothesis.

Meng *et al.* analyzed 417 COVID-19 patients admitted to Shenzhen Third People's Hospital, in China, from which 51 were hypertensive and, among them, 9 did not take any antihypertensive drugs. The 42 hypertensive patients who were taking antihypertensive medications were divided into two groups: those who used drugs such as ARB and ACE inhibitors (17 individuals) and those who used other classes of antihypertensive drugs, such as beta blockers or calcium channel antagonists (25 individuals). During hospitalization, 12 patients (48%) taking drugs other than ARB or ACE inhibitors had the severe form of COVID-19 and one of them died (27). On the other hand, among individuals who were taking ARB or ACE inhibitors, only 4 patients (23.5%) had the severe form of the disease and none of them died (27). Therefore, patients under treatment with ARB or ACE inhibitors were surprisingly less likely to have severe

symptoms of COVID-19, but this difference was not significant, probably due to the smaller number of subjects in this study. These patients were those who also had lower plasma levels of IL-6 (27), which is a proinflammatory cytokine involved in the pathophysiology of the host's excessive response to SARS-CoV 2 (39). In addition, the patients taking ARB or ACE inhibitors also had, during hospitalization, lower viral loads compared to individuals who used other classes of antihypertensive drugs (27). Given that higher viral loads have been linked to greater lung damage (40), it could be suggested that the use of ARB or ACE inhibitors might result in better prognosis.

Abajo *et al*. analyzed 1139 COVID-19 patients from different hospitals in Madrid, Spain, comparing them with 11390 controls. Among the 1139 COVID-19 patients, 237 were taking ARB, 240 were taking ACE inhibitors, 175 were taking any other antihypertensive drugs and 487 were not taking any hypertensive medications. The results indicated that the use of RAAS inhibitors was not related to a higher probability of requiring admission to the hospital by patients with COVID-19 (41). In another study, Li *et al*. analyzed 1178 COVID-19 patients, hospitalized in Wuhan, China, from which 30.7% (362) were hypertensive. Among the 362 hypertensive individuals, 115 were taking ARB or ACE inhibitors, while the other 247 hypertensive individuals were taking other classes of antihypertensive drugs or any antihypertensive drugs. It was observed that 49.6% of the patients under treatment with ARB or ACE inhibitors had the severe form of the disease and 18.3% died, whereas among the hypertensive individuals who were using other classes of antihypertensive drugs, 47% had the severe form of the disease and 22.7% died, indicating no relevant differences in morbidity and mortality between these groups (42). Mancia *et al*. analyzed 6272 COVID-19 patients, diagnosed between February 21 and March 11, 2020, in the region of Lombardy, Italy, comparing them with 30,759 individuals in a control group. It was found that the use of drugs that inhibit angiotensin II receptors and ACE inhibitors were not associated with a greater likelihood of SARS-CoV 2 infection (43). In addition, there was no relation between the use of these classes of drugs with more susceptibility to develop the severe form of COVID-19 (43).

Mehra *et al*. evaluated 8910 COVID-19 patients admitted to 169 hospitals from Asia, Europe and North America to establish a possible relation between the presence of cardiovascular diseases and use of specific pharmacological therapies with a higher mortality from COVID-19. Although it was established that the presence of cardiovascular diseases, such as hypertension, increases the possibility of developing the severe form of the disease, the use of different classes of antihypertensive drugs, such as

ARB and ACE inhibitors, was not related to a higher mortality in COVID-19 cases (44). Yang *et al.* analyzed 462 COVID-19 patients who arrived at Hubei Provincial Hospital of Traditional Chinese Medicine between January 5 and February 22, 2020; between these 462 individuals, 126 were hypertensive and they were divided into two subgroups: those who were taking ARB or ACE inhibitors (43 individuals) and those who were taking any other class of antihypertensive drugs (83 individuals); among patients who were using ARB or ACE inhibitors, 9.3% developed the severe form of COVID-19, while 22.9% of the individuals using other types of antihypertensive drugs had the severe form of the disease (45). A lower death rate (4.7% versus 13.3%) was seen in patients using ARB or ACE inhibitors when compared to individuals using other types of antihypertensive medications, although all differences did not reach statistical significance (45). In addition, the subgroup of hypertensive patients who were using RAAS inhibitors showed lower levels of C-reactive protein (CRP) (45), which has been related to a better COVID-19 prognosis and less severe lung injury (46), indicating that RAAS inhibitors could be acting in a protective way against lung damage related to COVID-19.

Semenzato *et al*. analyzed 2 million hypertensive patients and divided them into three groups: those taking ARBs; those taking ACE inhibitors; and those taking calcium channel blockers. Individuals who had any known risk factors for COVID-19 during the previous 5 years were excluded. Time to hospitalization and time to intubation or death were compared among the three distinct groups. Patients taking ACE inhibitors or ARBs had a lower risk of being admitted to the hospital, being intubated or dying when compared to individuals taking calcium channel blockers. Therefore, this study indicates that the use of ARBs and ACE inhibitors could actually be beneficial for these patients, and not harmful as previously suggested (47).

Table 1. Summary of clinical data regarding the use of RAAS inhibitors in COVID-19 patients.

Authors	Number of Patients	Main outcomes	Reference
Abajo *et al*.	ACEi/ARB: 477 Non ACEi/ARB: 175	No increased risk of requiring admission to the hospital was observed with either ACE inhibitors or ARB	(41)
Li *et al*.	ACEi/ARB:115 Non ACEi/ARB: 247	No relevant differences in morbidity and mortality was found between the individuals taking ARB or ACE inhibitors and the individuals taking other antihypertensive drugs	(42)
	ACEi/ARB:17	Patients taking ACE inhibitors or ARB had a lower probability of	

Meng *et al*.	Non ACEi/ARB: 25	developing the severe form of COVID-19, although it did not reach statistical significance. They also had lower plasma levels of IL-6 and lower viral load during hospitalization	(27)
Mancia *et al*.	ACEi/ARB:2896 Non ACEi/ARB: 736	No evidence was found to support that ARB or ACE inhibitors are able to affect the risk of COVID-19	(43)
Mehra *et al*.	ACEi/ARB:1272 Non ACEi/ARB: 497	The use of ARB and ACE inhibitors was not related to a higher mortality in COVID-19 cases	(44)
Semenzato et al.	ACEi/ARB: 1,524,303 Non ACEi/ARB: 358 306	The use of ARB and ACE inhibitors resulted in a lower risk of hospitalization, intubation or death	(47)
Yang *et al*.	ACEi/ARB:46 Non ACEi/ARB: 83	A lower proportion of critically ill patients and also a lower death rate were seen in individuals taking ARB or ACE inhibitors when compare to other antihypertensive drugs, although it failed to reach statistical significance. Also, individuals taking RAAS inhibitors had lower CRP levels	(45)

6 CONCLUSION

Although experimental and clinical data suggest that the use of RAAS inhibitors may result in overexpression of the SARS-CoV 2 receptor ACE-2, no clinical evidence so far indicates that chronic treatment with these drugs poses a major risk for COVID-19 patients. In fact, as exposed throughout this review, the use of these drugs could even have a protective mechanism against COVID-19, although further studies are still necessary. Thus, we believe that clinical evidence collected so far does not support any change in drug therapy used for hypertension during the current pandemic period.

AUTHORS AND CONTRIBUTORS

AFM, NSB and RRA wrote and revised the paper.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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