Title: SARS-CoV-2 infection & Cardiology: Overview on Renin-Angiotensin-Aldosterone System Inhibition.

Authors: Gustavo Henrique Sumnienski Bertoldi **1**, Rafael M. Ronsoni MD MsC **1**, Marcus Vinicius Magno Gonçalves MD PhD **1**.

1. Department of Medicine, University of the Region of Joinville, Santa Catarina, Joinville, 89202-207, Brazil.

Corresponding Author

Gustavo Henrique Sumnienski Bertoldi, student of University of the Region of Joinville. Rua Ministro Calógeras, 439, Bucarein, Joinville, Santa Catarina, Brazil, 892020-207. Phone number: +55 9 9107-1816. E-mail: gustavohen3@gmail.com

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Abstract:

The CoV-2 is a coronavirus strain, and its main way to get access to the cells is via the angiotensin converting enzyme 2 (ACE2) and cause the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). For the treatment of hypertension, it's commonly used angiotensin II receptor blockers (ARBs) and angiotensin II converting enzyme inhibitors (ACEIs). It's clear that there is still a lot of uncertainty and controversy around SARS-CoV-2 and ACE2 and only with more studies we will have proven answers. The use of medications such as ACEIs and ARBs should be individualized and in the majority of times its' suspension is not necessary.

Abbreviations

SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2

COVID-19 = Coronavirus Disease 2019

SARS-CoV= Severe Acute Respiratory Syndrome Coronavirus

SARS = Severe Acute Respiratory Syndrome

MERS = Middle-East Respiratory Syndrome

hRSV = human respiratory syncytial virus

SP or S protein= spike proteins

ACE1 = angiotensin-converting enzyme 1

ACE2 = angiotensin-converting enzyme 2

CoVs = coronaviruses

CoV-2 = novel coronavirus strain

RAAS=Renin-angiotensin-aldosterone system

Keywords

“SARS-COV-2”, “Covid-19”, “Renin–Angiotensin–Aldosterone System”, "Angiotensin-Converting Enzyme Inhibitors", "Angiotensin Receptor Blockers".

Background:

The SARS-CoV-2 outbreak initiated at Wuhan, China and in January of 2020, WHO declared global pandemic¹. Is a CoV-2 with similarities when compared its proteomics with SARS-CoV, and it main way to get access to the cells is via the angiotensin converting enzyme 2 (ACE2)^{1,2,3}. Since there is no treatment, nor vaccination to this specific etiological agent it resulted in a global shift in the researchers' objectives. Furthermore, medications that act in the renin-angiotensin-aldosterone system (RAAS), such as ACE, generate uncertainties regarding the maintenance of the use in heart diseases.

Regarding the use of ACEIs it is necessary to stress that even with structural similarities between ACE1 and ACE2, they have different activation sites and, therefore, ACE inhibition would not have a direct effect on ECA2 activity.

Angiotensin converting enzymes (ACE) role in the Renin-angiotensin-aldosterone system (RAAS).

RAAS is responsible for several physiological pathways, specially the blood pressure homeostasis. The first element of this system is renin. The majority of renin in the body is found in the juxtaglomerular cells of the kidney⁴. Renin cleaves angiotensinogen, which results in the production of angiotensin I. Another molecule in RAAS is angiotensin II, this is formed by angiotensin I cleavage by ACE. There are two main receptors for angiotensin II (AT1 and AT2), which are differentially expressed on the cell surface^{5,6,7}.

AT1 receptors are bound to G proteins, which mediates signaling pathways, such as activation of phospholipases, inhibition of adenylate cyclase⁶. These can lead to vasoconstriction, profibrotic action, growth stimulation and aldosterone release. Aldosterone increases sodium retention, thereby increasing blood pressure. The interaction of AT2 receptors and G proteins is controversial. AT2 receptor mediated signaling may antagonize AT1-mediated signal transductions⁷. However, accumulating evidence indicates that AT2 receptor-mediated signaling also mediates the detrimental action of angiotensin II.

Another RAAS-derived bioactive molecule is angiotensin-(1-7)⁴. The synthesis of angiotensin-(1-7) is mediated by a unique RAAS pathway involving ACE2, which is expressed predominantly in vascular endothelial cells of the heart and kidney⁴. Both ACE and ACE2 metabolize angiotensin I. However, the resulting peptides are different. ACE converts angiotensin I to angiotensin II, whereas ACE2 cleaves angiotensin I into angiotensin 1-9. Although angiotensin 1-9 itself exhibits no known biologic activity, angiotensin 1-9 is cleaved by ACE, and bioactive angiotensin-(1-7) is synthesized⁴. ACE2 can also directly cleave angiotensin II to form angiotensin-(1-7). Angiotensin-(1-7) plays a role as an antihypertensive molecule through the stimulation of the release of vasodilator prostaglandins and nitric oxides and inhibition of angiotensin II⁴.

Figure 1: Action of the renin-angiotensin system.

Management of high blood pressure and its repercussions on the patient.

Over 600 million people have high blood pressure⁸. In order to treat this disease, it's commonly used angiotensin II receptor blockers (ARBs) and angiotensin II converting enzyme inhibitors (ACEIs).

Studies by *Ferrario et al* have shown that ARBs (losartan) and ACEIs (lisinopril) increases the expression of ACE2 by 4.7 and 2.8 times in rats when blood pressure decreases, possibly increasing the virus potential of infection. This increase was found in heart and kidney cells¹; it's necessary new studies to see whether or not if this affirmation is also valid in pulmonary cells. ACEIs are known to reduce concentrations of angiotensin II, substrate for ACE2, being therefore more available¹. Lower expressions of this enzyme cause inflammation and lung edemas¹⁰.

A possible new approach to decrease the blood pressure is the use of direct renin inhibitors (DRIs). It has been shown that DRIs diminish the activity of the RAAS and also downregulate ACE2 in animal models, subsequently lowering the infection potentials¹¹. Thereby with DRIs, cardio-pulmonary protection is maintained and ACE2 seems to be downregulated¹². ALTITUDE trial in patients with type 2 diabetes found increased cardiovascular risks on combining aliskiren with either ACE inhibitors or ARBs¹².

COVID-19 effects in cardiovascular tissue

Some studies suggest that cardiovascular injuries secondary to the virus could be related to ACE2^{11,13}. Hence, ACE2 regulates negatively angiotensin II, having a protective role against respiratory insufficiency and its progression¹¹. SARS-CoV-2 contains four main structural proteins: nucleocapsid protein (N), spike protein (S), protein envelope (E) and membrane protein (M). The virus binds via the spike protein to the ACE2 receptor and, through this link, enters the host cell, where ECA2 inactivation occurs, which favors lung injury¹³. As ACE2 has high concentrations in the heart, potentially serious damage to the cardiovascular system can occur.

Patients with preexisting cardiovascular diseases seem to have higher ACE2 serum levels, which could lead to more harsh manifestations of COVID-19¹⁴⁻¹⁶. Likewise, individuals with high blood pressure express a higher ECA2 concentration due to ACEIs or ARBs usage, which could increase the chances of infection¹⁷. It's necessary to stress that even with these results, we have to be careful, since the number of individuals tested was low, and the majority of them were old¹³.

Uncertainties around ACE 2 and COVID-19

A lot of the physiological and biochemical mechanisms of COVID-19 are still uncertain, however we can already have some intake into interesting paradoxical events that are found in SARS-Cov-2 patients. One of the main topics of controversy is the fact that the disease tends to infect more and be more deadly in the elderly and in patients with comorbidities (such as hypertension and diabetes). It's interesting that in *Cheng* study, the older the person is, the lower the expression of ACE2 is found, which would theoretically be less prone to infection. It's relevant to show that hypertension patients naturally have higher expression of ACE2 and therefore can be infected more easily, theoretically.

An important finding described by *Vaduganathan (2020)* is that the level of circulating ACE2 is usually low, and its main function is being performed mainly in the lungs of healthy individuals, which would make it harder to infect individuals. The idea that the higher the concentration of ACE2, the higher are the chances of contracting the virus is overthrown by *Vaduganathan (2020)* study. This study states that 35% of patients who die by COVID-19 showed the presence of viral RNA, which in turn was associated with reduced ACE2 protein expression.

Clinical practice

Considering the disease's spread, lethality and treatment as easy tasks to take care of is extremely naive, since all the data collection was done in a short period of time, giving us a shorter time to evaluate, comprehend and develop around these findings. It's clear that more investment and effort are needed to develop scientifically proven medications and vaccines¹¹.

The treatment with ACEIs and ARBs has been shown that it can up-regulate ACE 2 receptor expression and it's thereby theoretically possible that pre-existing use of these drugs might predispose a person to infection with a greater viral load of SARS-Cov-2 as a result of greater ACE 2 expression²⁰.

Even with those findings, the American Heart Association does not recommend the interruption of ACEIs and ARBs^{19,21}. *Aronso JK et al* suggest the adoption of the protocol underneath to the management of patients in the SARS-CoV-2 context²².

Figure 2, adapted from: Drugs and the renin-angiotensin system in covid-19 *BMJ* 2020

Zhang P et al published a retrospective multicenter study conducted in Chinese in-hospital centers use of ACEI/ARB was associated with lower risk of all-cause mortality due to COVID-19

compared with either nonuse of ACEI / ARB (adjusted HR, 0.37; 95% CI , 0.15-0.89; P = 0.03) .or use of a different class of anti-hypertensive agent (adjusted HR, 0.30; 95% CI, 0.12-0.70; P = 0.01) in COVID-19 patients with hypertension, it is important to highlight possible biases associated with retrospective²³. However, we can utilize these findings to defend the recommendations done by several cardiology societies. The protective effect of ACEI/ARB also may result from the favorable effect on microvascular complications, this reduces cardiovascular and renal morbidity²³.

New patients could be treated with DRIs, since these drugs diminish the expression of ACE2¹, but without a proven level of evidence. There is currently no effective drug for the treatment of SARS-CoV-2, and it's speculated that ACE2 spike protein-based vaccine and rhACE2 may become one of the most promising approaches, improving the prognosis of patients with this viral infection¹⁸. One thing is almost consensual is that consumption of ACE2 by the virus could increase the activation of the RAAS.

Conclusions:

It's clear that there is still a lot of uncertainty and controversy around SARS-CoV-2 and ACE2 and only with more studies we will have proven answers. The utilization of ACEIS and ARBs medications should be individualized and in the majority of time its' suspension it's not necessary.

This pandemic has less severe lethality, and different spread rates when compared to the Spanish flu and Bubonic plague. However, we cannot underestimate the changes that our society, economics, relationships and education are suffering. Getting close to a new medication or even a vaccination will demand a collective effort.

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