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LETTER TO THE EDITOR

Relationship between renin-angiotensin system and novel coronavirus infection (COVID-19)

Relación entre sistema renina angiotensina e infección por COVID−19

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Dear Editor:

We recently read the editorial of the last issue of the *Revista Habanera de Ciencias Médicas* (Volume 19 Number 2 January-February, 2020) entitled "Severe acute respiratory infection (COVID-19): an imminent threat"[(1)] and we wanted to comment on it.

The pandemic of the new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), also called COVID-19, was undervalued by most countries and especially by the main nations of the western hemisphere, since their National Security Services knew about

the germ and its disastrous effects since before the world identified the severity of the pandemic. Those governments reported that they had the control of the virus, while evidence demonstrated that it was the virus the one that had the control over the population.

This delayed reaction overstated the devastating effect of COVID-19 and ruined the health systems of developed countries, considered solid up until then.

Currently, the scientific community is experimenting with multiple drugs in hopes of better results against a new virus that spreads in the human body through the receptors of the renin-angiotensin system. However, the paradox arises regarding the indication of drugs that inhibit this system and that are first-line drugs in cardiovascular therapy.

The COVID-19 causes severe respiratory syndrome and higher mortality than the pandemics that preceded it caused by other coronaviruses.[2] The lethality for this condition in the world is around 5 % and affects more frequently those patients suffering from high blood pressure, cardiovascular diseases, diabetes mellitus, kidney failure, immunosuppression and older patients, as demonstrated by the largest study carried out in China.[3]

Pathophysiology (Figure 1)

As described in Wuhan,[2,4] it is a severe acute respiratory syndrome similar to its previous SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome coronavirus) that occurred in 2002, 2003, 2012 and 2013. The virus penetrates through the eyes, the nostrils and the mouth. It goes to the throat where it stays for 3 or 4 days producing cough, sore throat, fever, respiratory distress, gastric problems and diarrhea. Subsequently, it reaches the lungs with diffuse bilateral alveolar injury, cellular fibromyxoid exudate associated with degeneration, parenchymal cell necrosis with hyaline thrombus formation in small vessels extensive to the liver, heart, splenic region with lymphedema, and cellular degeneration.

Two electron microscopy studies demonstrated the binding of the protein S of the virus to the angiotensin converting enzyme II (ACE II) receptor protein at the level of the respiratory cell surface, causing a systemic inflammatory reaction in the body and generating an imbalance of the renin-angiotensin system with an increase in angiotensin-II (A-II) in correspondence with the elevation of the viral load.[5,6,7]

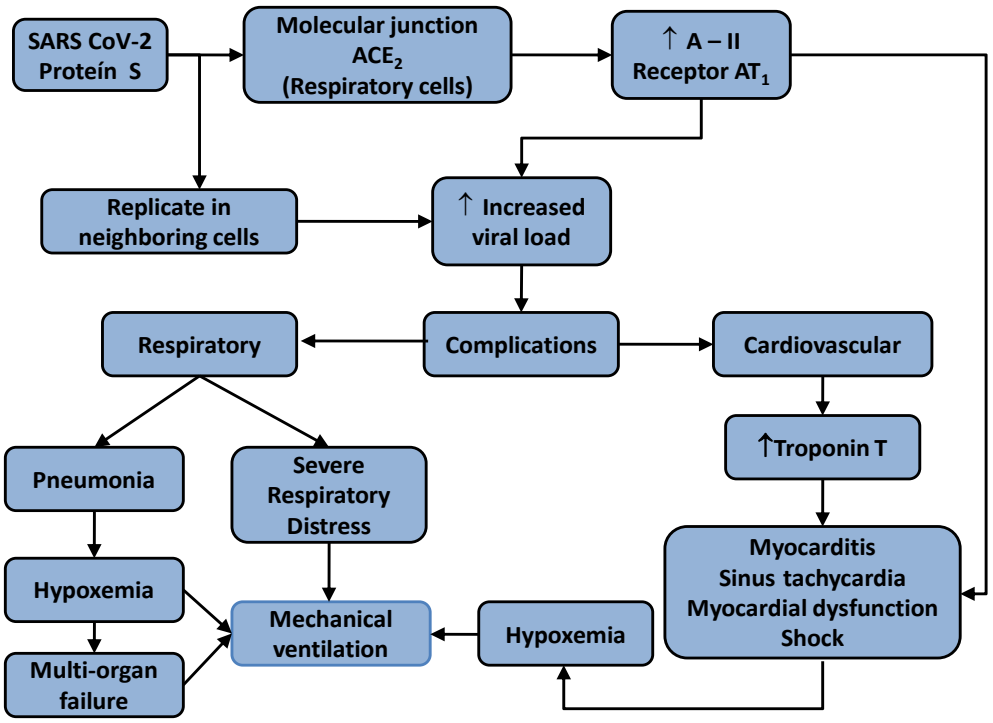
The higher viral load, the greater tissue damage with acute respiratory distress syndrome (ARDS). High levels of A-II have been observed in severe cases of COVID-19, so some research suggest that the indication of angiotensin II receptor antagonists (ARA-II) is beneficial in these patients.[5]

Tissue A-II behaves as a hormonal mediator since it exerts endocrine actions when it is released into the bloodstream and produces effects on the body; it has a paracrine action on neighboring cells; autocrine action when doing it on receptors of the own cell wall and intracrine action when it acts on the intracellular components that originate A-II. This actions of A-II could explain the rapid spread through its receptors that are located almost everywhere in the body.

The high incidence of cardiovascular symptoms in

COVID-19 infection is related to the systemic inflammatory response, with the effect of dysregulation of ACE II, with the respiratory dysfunction itself and hypoxia; which adds to the possibility of acute damage to myocardial cells.[8,9]

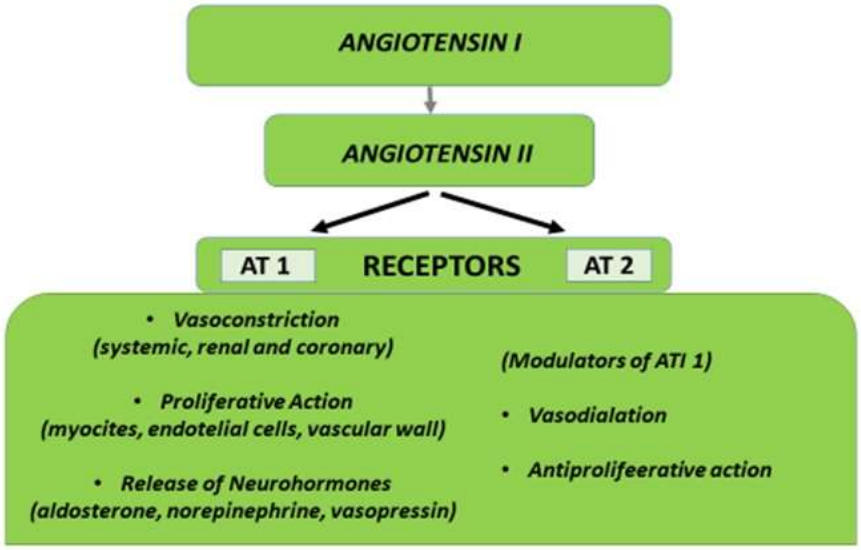
Fig. 1 - Pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)



Angiotensin- II receptor types and actions [10]

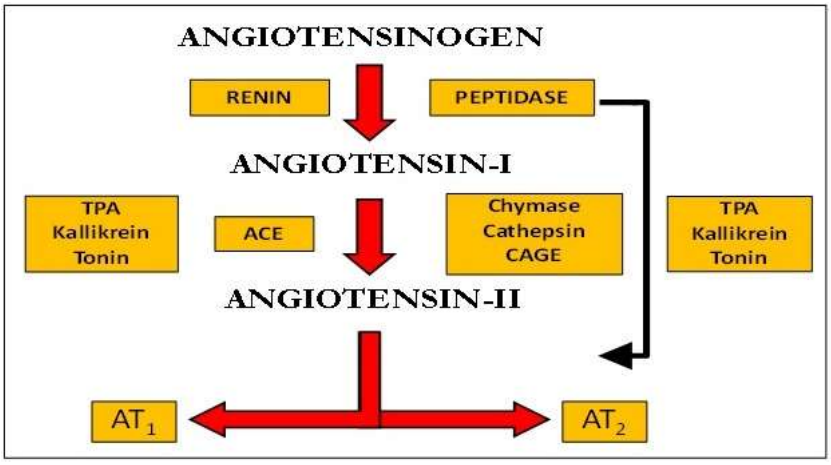
A-II is a substance that regulates blood pressure and hydrosaline homeostasis and is directly related to the genesis of Hypertension (HT), Ischemic Heart Disease (IHD), congestive heart failure (CHF) and kidney failure (KF). A-II mainly acts on AT_1 and AT_2 receptors that are located on the target organs and on the vascular wall. These receptors have opposite effects. (Figure 2). In HT and CHF, the consequences of stimulation of AT_1 receptors predominate.

Fig. 2 - Angiotensin-II receptor types and actions



In the synthesis of A-II, a classic pathway is recognized through ACE II while other syntheses of ACE-II independent pathways are capable to convert Angiotensinogen in A-II directly, or in AI and then A-II. (Figure 3).

Fig. 3 - A-II synthesis pathways independent of the ACE



The renin-angiotensin aldosterone system is currently being investigated. Different hypotheses provide new insight into an additional pathway in which a widespread form of angiotensin I, proangiotensin-1, 2, may be an alternative active biological substrate for angiotensin production.

Chymase produces 90 % of A-II in the human heart; therefore, the blockade of angiotensin converting enzyme inhibitors (ACEI) is not

complete.

Angiotensin-II actions in the heart:

1. Activation of the caspase cascade: programmed cell death or apoptosis.
2. It induces necrosis.
3. Fibrosis.
4. Myocardial hypertrophy.
5. Promotes the accumulation of interstitial collagen in the heart.
6. They are involved in ischemia-reperfusion injury.
7. In the post-acute myocardial infarction stage, it causes ventricular remodeling of the non-infarcted muscle that becomes hypertrophic or fibrous due to vasoconstriction, proliferation and cell growth caused by A-II.
8. In rats, the AT_1 / AT_2 receptors are present in similar proportions.
9. In the human heart, AT_2 duplicate AT_1, but in terminal CHF, A-II receptors decrease more than 50 % at the expense of AT_1. The receptors are altered in various cardiomyopathies and, as it has been shown, they are not located in the myocytes but in the fibroblasts.
10. Regulates intrarenal hemodynamics, glomerular filtration, and tubular reabsorption of solutes and water.

It releases aldosterone in the adrenal cortex and increases sodium reabsorption in the distal nephron, increasing total peripheral resistance and vasoconstriction, which contributes to the pathogenesis of diabetic nephropathy and perpetuates hypertension.

Renin angiotensin system inhibitors

All of these patients require ACEI and/or ARA-II therapy for better control of their disease and this indication is the subject of intense debate and future research in patients with COVID-19 or at risk of the disease.

In conjunction with initial reports from China[(2)] and from other countries with regard to the fact that hypertension was a higher risk of mortality in hospitalized patients with COVID-19, hypotheses arose about possible adverse effects of ACEi and ARA-II.[(3)] The suggestion, especially in social networks, was that these medications could increase the risk and severity of SARS-CoV-2 infection. According to the Council of the European Society of Cardiology and Hypertension, the speculation about the safety of treatment with ACEi and ARA-II has no solid scientific basis or supporting evidence.

There are animal studies showing that drugs related to the renin-angiotensin aldosterone system have a protective effect against serious pulmonary complications caused by coronavirus; but to date, it has not been demonstrated in humans.[(11)]

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Conflict of interests

The authors declare that there is no conflict of interests.

Author contribution

JSC: Research design and bibliographic review.

ESS: Main idea of the research and literature search.

LSF: Compilation of data.

ESPP: Design of figures.

All authors participated in the bibliographic search, the scientific writing, and all of them have approved the final version of the text.