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RAS AND SARS-CoV-2 INTERACTION: SHORT REVIEW OF THE LATEST EVIDENCE

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Abstract. Coronavirus SARS-CoV-2 is responsible for the coronavirus disease (COVID-19) cause of the recent global pandemic, which is causing thousands of deaths worldwide and represents a health challenge with few precedents in human history. The angiotensin 2 conversion enzyme (ACE-2) has been identified as the receptor that facilitates access to SARS-CoV-2 in cells; evidence shows that its concentration varies during the various stages of viral infection. Therapeutic agents modifying the renin-angiotensin system (RAS) may be able to modulate the concentration of ACE-2 and the various components of the system. In this article we examine the latest evidence on the association between the use of RAS modifying agents and coronavirus 2019 (COVID-19) disease caused by SARS-CoV-2. Our investigation and critical literature research does not suggest discontinuation of ACEIs/ARBs treatment in clinical practice as there is a lack of robust evidence. However, we recommend further well-structured epidemiological studies investigating this sensitive issue that may provide important new suggestions for implementing guidelines.

Key words: *COVID-19, renin-angiotensin system, SARS-CoV-2, pandemic.*

ВЗАИМОДЕЙСТВИЕ SARS-CoV-2 И РЕНИН-АНГИОТЕНЗИНОВОЙ СИСТЕМЫ: КРАТКИЙ ОБЗОР ПОСЛЕДНИХ ДАННЫХ

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Резюме. Коронавирус SARS-CoV-2 является причиной коронавирусной болезни (COVID-19), вызвавшей недавнюю глобальную пандемию, которая унесла тысячи жизней во всем мире и представляет собой проблему для здоровья, имеющую лишь несколько прецедентов в истории человечества. Ангиотензинпревращающий фермент 2 (ACE-2) был идентифицирован как рецептор, который облегчает доступ к SARS-CoV-2 в клетку; данные показывают, что его концентрация варьируется на разных стадиях вирусной инфекции. Терапевтические агенты, модифицирующие ренин-ангиотензиновую систему (РАС), могут быть способны модулировать концентрацию ACE-2 и различных компонентов системы. В этой статье мы исследуем последние доказательства связи между использованием агентов, модифицирующих RAS, и COVID-19. Наше исследование и данные литературы не предлагают прекращения лечения ACEIs/ARBs в клинической практике, поскольку для этого отсутствуют надежные доказательства. Тем не менее мы рекомендуем провести дальнейшие хорошо структурированные эпидемиологические исследования этой деликатной темы, результаты которых могут способствовать появлению новые принципов терапии COVID-19.

Ключевые слова: *COVID-19, ренин-ангиотензиновая система, SARS-CoV-2, пандемия.*

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The SARS-CoV-2 (COVID-19) virus is responsible for the current global pandemic, causing thousands of deaths and responsible for a health challenge with few precedents for humanity. SARS-CoV-2 is a family of RNA viruses capable of infecting humans and causing respiratory distress syndrome with severe lung injury in some fatal cases [2]. Studies have shown that SARS-CoV-2 has about 80% of the SARS-CoV-like genome responsible for the 2003 outbreak [4, 6]. Evidence shows that viral infection has several stages: in the first stages an asymptomatic or slightly symptomatic clinical course is described, the subsequent moderately severe stages characterised by a pulmonary inflammatory state, the last very severe stages characterised by a generalised inflammatory state affecting all tissues causing multi-organ dysfunction and in some cases death [1]. Biochemical interaction studies have shown that SARS-CoV-2 virus enters host cells mainly through the use of the spike protein (S) [10, 11] through the angiotensin 2 conversion enzyme receptor (ACE-2) on the cell surface [10]. ACE-2 is also a conversion enzyme that is part of the renin-angiotensin system (RAS). Is there a scientific debate going on since the beginning of the pandemic, is an increase of ACE-2 responsible for a higher probability of COVID-19 infection? Lung tissues are probably an easier entry route for SARS-CoV-2 because 83% of ACE-2 receptors are present in type II pneumocytes that produce surfactants that prevent to the alveoli to collapse [12]. The RAS modulating drugs are widely used in the treatment of cardiovascular diseases, but what is the correlation between these drugs, RAS and COVID-19? Can they play a protective role by modulating the expression of RAS components? Or, on the contrary, are these drugs considered risk factors for COVID-19?

To date, it is strongly recommended not to interrupt the treatment with the usual therapy of RAS modulating drugs, because no clinical or scientific evidence suggests this [3]. Agents acting on RAS can be distinguished as inhibitors of the angiotensin conversion enzyme (ACEI), Angiotensin II receptor blockers (ARB) and direct renin inhibitors (DRI) (Bavishi et al., 2020). These agents are currently indicated for the treatment of various cardiovascular diseases with excellent clinical efficacy. ACEIs are able to reduce blood pressure by acting with ACE inhibition which converts Ang I to Ang II. ARBs are Ang II antagonists on the type 1 receptor (AT-1r), finally, DRIs block plasma renin activity and inhibit the conversion of angiotensinogen to Ang I. The three different classes described above have different effects on the regulation and enzymatic expression of RAS [9]. A retrospective epidemio-

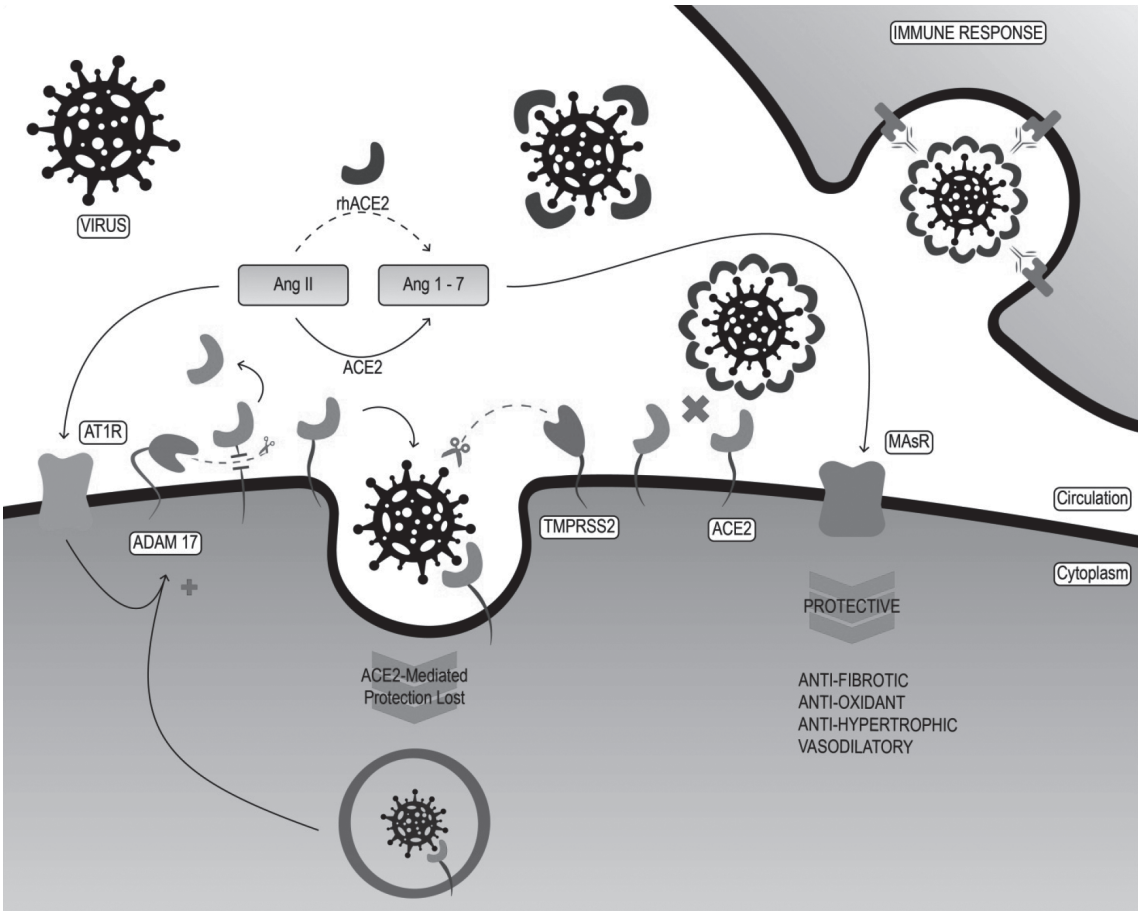

Figure. SARS-CoV-2 and ACE-2 interaction
Comments. SARS-CoV-2 penetrates cells by binding the peak viral protein (S) to ACE-2. ACE-2 converts Ang II to Ang 1–7. Ang 1–7 has opposite biological actions to Ang II, antifibrotic, antioxidant and antihypertrophic effects through the stimulation of MasR.

logical cohort study using database data showed that the use of ACEI or ARB was not significantly associated with mortality and diagnosis of COVID-19, respectively [5]. Another study using electronic health records from the University of New York (NYU) Langone Health showed no significant correlation and association between the use of ACEI/ARB and the development of COVID-19 and COVID-19 severe, respectively [7]. In addition, another retrospective and multicentre study conducted on a large scale in adult hypertensive patients with COVID-19 in Hubei, China 9, showed that the use of ACEI or ARB was significantly associated with a lower probability of mortality due to different causes than non-users of ACEI/ARB, probably for a greater and more effective management of underlying cardiovascular disease in the patients considered. Finally, some studies have not been considered because they show inconsistent data [13]. In addition, in several studies, investigations in patients receiving ACEi or ARB treatment did not have higher plasma concentrations and significant changes in ACE-2, in contrast to in vitro data [8]. In conclusion, based on currently available data and taking into account evidence of reduced mortality in cardiovascular disease, ACE-I and ARB therapy should be maintained or initiated in patients with cardiovascular disease according to current guidelines of the major scientific societies.

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