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Letter to the Editor

Letter in response to the article: Comorbidities in COVID-19: Outcomes in hypertensive cohort and controversies with renin angiotensin system blockers (Singh et al.)

To the Editor

Dear Sir.

We read with great interest the recently published article in this journal by Singh A.K et al. [1], regarding the controversies surrounding the use of RASB (Renin-angiotensin system blockers) among hypertensive patients in the COVID-19 (coronavirus 2019) era. Though we agree with the authors on most parts of the review, we have few concerns regarding the rationale and mechanisms for benefit of RASB in COVID-19 (section 3.5 b). We agree with one of the proposed mechanism that involves an increase in the soluble form of ACE-2 (Angiotensin-converting enzyme-2), which acts as an interceptor by binding to SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2) and does not allow the virus to bind to the membrane bound ACE-2 receptor, thereby inhibiting viral entry inside the cell [1–3]. However, we do not agree with the other proposed mechanism whereby authors have suggested that "RAS blockers increase angiotensin II, which is a substrate for ACE-2.

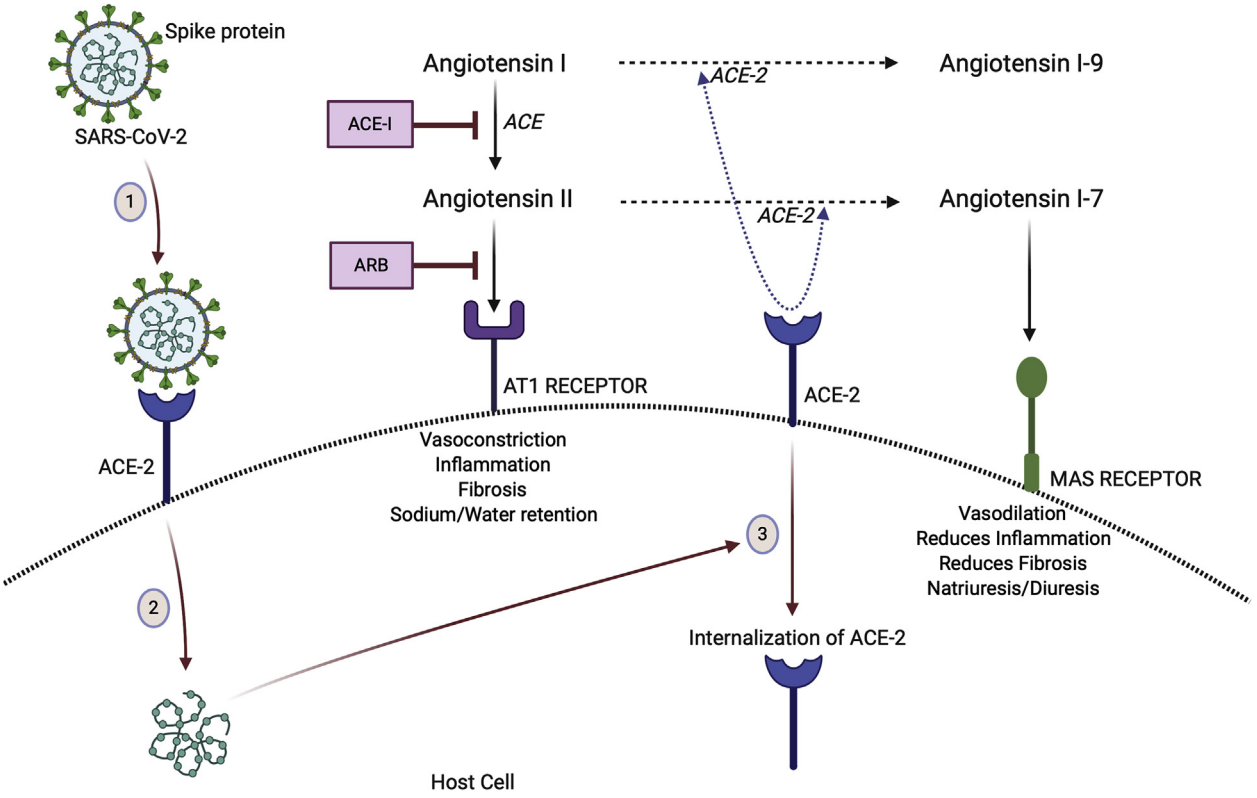

Fig. 1. A proposed mechanism of benefit with renin-angiotensin system blockers in SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) associated tissue injury. SARS-CoV-2 enters the host epithelial cells (1) through the interaction of its spike protein with the functional receptor "ACE-2" (angiotensin converting enzyme-2). After cell entry, viral replication takes place (2) which simultaneously downregulates the membrane bound ACE-2 receptors and causes their internalization (3). The reduced expression of ACE-2 leads to unopposed action of angiotensin II on its AT1 (angiotensin II type 1) receptor. This results in increased inflammation, fibrosis, vasoconstriction, oxidative stress, and aldosterone mediated sodium and water retention, subsequently resulting in acute lung injury. Diminished production of angiotensin II with an ACE-I or blockade of AT1 receptor with an ARB enhances the generation of angiotensin (1–7) by ACE-2 and activation of the MAS receptor, which attenuates harmful effects of angiotensin II and therefore attenuates lung injury.

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The interaction of ACE-2 with angiotensin II could induce a conformational change in the receptor binding domain of ACE-2, limiting its ability to bind with SARS CoV2." We do not agree with the above explanation since ACE-I (Angiotensin-converting enzyme inhibitors) and ARB (Angiotensin II receptor blockers) have differential effects on the levels of angiotensin II [3,4]. While ACE-Is inhibit the conversion of angiotensin I to angiotensin II, thereby decreasing its levels, ARBs block the angiotensin II receptor and usually cause no change in levels of angiotensin II with short term use. However, the chronic long-term use of ARB does cause elevation in the levels of angiotensin II [3,4]. Therefore, if we believe in the proposed mechanism that increased angiotensin II brings conformational change in ACE-2, and limits its binding ability to SARSCoV-2, this would mean a lower infection risk with ARBs and a higher infection risk with ACE-I. This hypothesis looks unrealistic and will need further validation. Unfortunately, the authors have not highlighted an important proposed mechanism of protection by RASB against SARS-CoV-2 associated lung injury. Based on the in-vitro studies done with other coronaviruses, it is believed that after the SARS-CoV-2 enters the alveolar cells using membrane bound ACE-2, it further downregulates the expression of ACE-2 receptors on the membrane and causes their internalization [2,3,5] (Fig. 1). As a result, the ACE-2 dependent conversion of angiotensin II to angiotensin (1–7) decreases, leading to an increased level of angiotensin II and a decreased level of angiotensin (1–7). Angiotensin II then acts unopposed through its receptor AT1R (angiotensin II type 1 receptor) to induce cellular inflammation, proliferation, oxidative stress, vasoconstriction, fibrosis, and aldosterone activation, subsequently resulting in lung injury [3]. Angiotensin (1–7), which acts via MASR (Mas receptors), acts in the opposite direction to that of angiotensin II, and has anti-inflammatory, anti-fibrotic, vasodilatory effects and eventually protects against lung injury [3]. (Fig. 1) So the SARS-CoV-2 infection causes downregulation of ACE-2 and skews the local renin-angiotensin system towards the injurious "ACE-Angiotensin II-AT1R axis" instead of the protective "ACE2-Angiotensin (1–7)- MASR axis" and results in lung damage. This mechanism of lung injury with SARS-CoV-2 is further supported by a small study, in which patients with Covid- 19 appeared to have elevated levels of plasma angiotensin II, which were in turn correlated with total viral load and degree of lung injury [6]. It is hypothesized that the use of RASB would protect against this lung injury by two pathways. First, the use of RASB might result in overexpression of membrane bound ACE-2, thus acting against the downregulation caused by the coronavirus [3]. Secondly, the inhibition of the synthesis of angiotensin II by ACEIs and blockade of its AT1R by ARBs, would skew the local RAS axis towards the protective "ACE2-Angiotensin (1-7)-MASR", and minimize the risk of lung injury (Fig. 1). This hypothesis finds support from an experimental mouse model, where exposure to SARS-CoV spike protein induced acute lung injury, which was mitigated by the RAS blockade [7]. However, it must be emphasized that all discussion surrounding RASB in SARS-CoV-2 infection is predominantly based on hypothetical mechanisms which have been derived largely from the experimental animal studies, and would need focused future prospective human studies to precisely define the interplay between RASB and SARS-CoV-2 infection. Till then it's prudent to continue the use of RASB for the treatment of hypertension as recommended by various society guidelines. Furthermore, trials are underway to test losartan (an ARB) as an effective therapy for COVID-19 [3].

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