Renin Angiotensin System and Coronavirus Disease 2019 (COVID-19): An updated review

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Abstract
Abnormal Renin-Angiotensin System (RAS) activation has a pivotal role in pathogenesis of cardiovascular or metabolic diseases, known risk factors for poor outcomes in COVID-19. An additional tissue RAS imbalance through interaction of ‘severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2) with angiotensin-converting enzyme 2 (ACE-2) seems to play a role in pathogenesis of COVID-19. This interaction has raised some questions about safety of RAS-inhibitors use in COVID-19 patients. On the other hand, potential benefits of RAS-inhibitors use have been suggested. This article presents a brief updated review of renin-angiotensin system (RAS) focusing on interaction with SARS-CoV-2 infection, potential risks or benefits of RAS-inhibitors use, and RAS-related therapeutic targets in COVID-19.

Keywords: Coronavirus disease 2019, COVID-19, angiotensin-converting enzyme 2, renin-angiotensin system, renin-angiotensin system blockers

Introduction
In December 2019, a novel coronavirus capable of infecting and causing disease in human species emerged in Wuhan city (China) and spreads rapidly across the world [1]. As of July 19, 2020, a total of 14360451 confirmed cases and 603378 deaths had been reported in 188 countries/regions worldwide [2], and the numbers continue to rise.

The new coronavirus has been officially named “severe acute respiratory syndrome (SARS) coronavirus 2” or SARS-CoV-2, by similarity to coronavirus SARS-CoV, which caused an outbreak of SARS in 2003. The coronavirus disease caused by SARS-CoV-2 was named “coronavirus disease 2019” or COVID-19 [3].

COVID-19 has a broad clinical spectrum ranging from mild upper respiratory tract symptoms in most cases to severe pneumonia and acute respiratory distress syndrome (ARDS) with respiratory failure, the main cause of morbidity and mortality [4,5]. Hypertension and cardiovascular diseases, as other comorbidities, have been identified as risk factors for developing severe disease and increased mortality [4-7].

Recent knowledge that novel coronavirus SARS-CoV-2, like coronavirus SARS-CoV, uses angiotensin-converting enzyme 2 (ACE-2) as receptor to entry into host cells [8,9], has rapidly pushed up concerns about safety of renin-angiotensin system inhibitors use, by potential ability to increase ACE-2 expression, hypothetically favouring virus entry and disease virulence in cardiovascular patients [10-13].

The purpose of this article is to summarize an updated review of renin-angiotensin system focusing on interaction with SARS-CoV-2 infection, potential risks or benefits of RAS inhibitors use, and RAS-related therapeutic targets in COVID-19. An electronic search was performed in Medline (PubMed interface) using the keywords: coronavirus, coronavirus disease 2019, COVID-19, SARS-CoV-2, angiotensin-converting enzyme 2, ACE2, renin-angiotensin system, renin-angiotensin system blockers, cardiovascular system, cardiovascular disease, and their various combinations, between 2019 and June 30, 2020. Additional articles were obtained of references in the selected articles.

Review
Renin-Angiotensin System revisited
The renin-angiotensin system has a central role in normal physiology regulating hydroelectrolytic balance and blood pressure. Also, RAS plays a critical role in pathogenesis and pathophysiology of cardiovascular disease [14-16]. In modern concept, RAS has two pathways that mutually influence each other: the classical and alternate pathways. Cardiovascular homeostasis results from the balance between these dual effects. Circulating RAS coexists with a local or tissue RAS [14,17-19].
Classical RAS axis: ACE / Angiotensin II / AT1-receptor
Major components of the classical axis include: angiotensinogen, renin, angiotensin I, angiotensin II and the angiotensin-converting enzyme (ACE). Angiotensin II is the principal effector of the classic axis [14,17,18].

The substrate of the system is angiotensinogen, a protein synthesized and released into circulation from the liver. Angiotensinogen is converted to angiotensin I by renin, secreted by the juxtaglomerular apparatus of the kidney. Subsequently, angiotensin I is converted to angiotensin II by angiotensin-converting enzyme. ACE is expressed in high quantities on the surface of the vascular endothelial cells of pulmonary circulation. Beside of the lungs, ACE is expressed, to a lesser extent, in other tissues: kidney, intestine, placenta, choroid plexus and testis [14,17,18].

Angiotensin II is the most potent regulatory peptide of the classical axis exerting its biological effects through two cellular receptors: angiotensin type-1 (AT1) and angiotensin type-2 (AT2) receptors. Angiotensin II acts mainly through AT1 receptor. AT-1 receptor activation causes vasoconstriction, hypertrophy, inflammation, and apoptosis. AT-2 receptor activation results in vasodilation, as well as anti-inflammatory and antiproliferative effects. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, which partakes in hydroelectrolytic and blood pressure homeostasis, but may also lead to pathological effects, mainly tissue fibrosis and oxidative stress [14-19].

Angiotensin II is metabolized in few minutes by angiotensin-converting enzyme 2 (ACE-2), which has a pivotal role in the alternate RAS axis [17,20].

Alternate or counter-regulatory RAS axis: ACE-2 / Angiotensin 1-7/Mas-receptor
Components of this counter-regulatory axis include: angiotensin-converting enzyme 2, angiotensin 1-7 and its proto-oncogene Mas receptor [17,18].

ACE-2 is a membrane bound protein that has an extracellular domain with catalytic activity against angiotensin I (producing angiotensin 1-9) and angiotensin II (producing angiotensin 1-7). The ACE-2 catalytic efficiency for AT-II is almost 400 times greater that for AT-I, so angiotensin 1-7 is the main product of ACE-2 activity [17,18,21].

Angiotensin 1-7 can also be generated from angiotensin I. In a first step, ACE-2 hydrolyses AT-I to generate angiotensin 1-9, which is subsequently hydrolysed by ACE to generate angiotensin 1-7 [17].

The physiological role of angiotensin 1-7, the main active product of the alternate axis, has not yet fully elucidated, but data suggests that plays a crucial role in counteracting the damaging effects of AT-II. Angiotensin 1-7 has been shown to be beneficial through its vasodilatory, antithrombotic and antiproliferative effects, mainly mediated by its interaction with Mas receptor and probably also with AT2 receptor [14,17,22-24].

The catalytic domain of ACE-2 shares 42% identity and 61% similarity to catalytic portion of ACE, but is not inhibited by classical ACE inhibitors (ACEIs) [23,25]. The membrane-bound extracellular domain of ECA-2 can be cleaved by the metallo-proteinase ADAM17, which release a soluble form of ACE-2 [17].

ACE-2 is present in a wide variety of cells and tissues, with increased expression in vascular endothelial cells, lung, heart, and kidney. It has also been described in the gastrointestinal system, nervous system and testis [17,20,22,24]. In the lungs, ACE-2 was found in alveolar epithelial cells, mainly in type II pneumocytes [22,26].

In addition, ACE-2 has been identified as receptor for novel coronavirus SARS-CoV-2 [9].

The SARS-CoV-2/RAS interaction
SARS-CoV-2 is a spherical enveloped, positive-sense, single-stranded RNA betacoronavirus, characterized by presenting spicular crown-shaped projections. The SARS-CoV-2 genome shares about 80% identity with that of SARS-CoV and is almost 96% identical to a bat coronavirus [27,28].

Coronavirus spike protein (S protein) facilitates binding and viral entry into target cells. S protein is conformed of 2 subunits: S1 and S2 subunits. S1 subunit facilitates viral attachment to the cell surface receptor, but entry requires S protein processing (priming) by a protease to expose S2 subunit, which ultimately facilitates fusion of viral envelope with cell membrane, allowing virus entry. The novel coronavirus SARS-CoV-2, like SARS-CoV, uses ACE-2 as membrane receptor and employs the membrane protease TMPRSS2 for S protein priming. S protein priming by TMPRSS2 protease is essential for viral entry into host cells [8,9,27,28].

The S protein/ACE-2 interaction seems to plays an important role in the pathogenesis of lung injury, the main determinant of morbimortality in coronavirus SARS-CoV and SARS-CoV-2 infection. In experimental models, both SARS-CoV infection and isolated S protein infusion produce a considerable downregulation of pulmonary ACE-2 expression, without affecting pulmonary ACE expression. This would modify tissue RAS balance, favouring deleterious angiotensin II effects on lung tissue [29].

COVID-19 and Renin-angiotensin system inhibitors
RAS activation is known to play a critical role in the pathogenesis of cardiovascular diseases. Therefore, trying to modulate pathogenic effects of AT-II, RAS inhibitors are the cornerstone of pharmacological intervention. Classical RAS inhibitors, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin type 1 receptor blockers (ARBs) have shown robust evidence of their beneficial effects on cardiovascular morbimortality [30-32]. Although classical RAS-inhibitors do not inhibit ACE-2 activity, have shown be able to increase tissue ACE-2 expression in animals [33-36] and humans [37,38]. This effect has triggered concerns about a greater vulnerability to SARS-CoV-2 infection among cardiovascular patients receiving these agents.
COVID-19: Evidence for potential deleterious effects of RAS inhibitors

Knowledge of SARS-CoV-2 / ACE-2 interaction has raised questions about safety of RAS-inhibitors in COVID-19 patients. So far, the only argument put forward to support a hypothetical higher vulnerability to COVID-19 in RAS inhibitors users has been the ability of these agents to increase ACE-2 expression, which also acts as receptor for SARS-CoV-2 [10-13]. However, so far there is no evidence that this effect facilitates viral entry or increases disease virulence [39,40,48]. In vitro, only one of seven ACE-2 expressing cell lines was susceptible to coronavirus SARS-CoV infection, despite this cell line had an intermediate ACE-2 expression compared to each other, suggesting that ACE-2 by itself is insufficient to explain the coronavirus infectivity [49].

Several retrospective analyses have been published regarding the safety use of these drugs on COVID-19 patients. Taken together, provide convincing evidence that RAS inhibitors use is not associated with an increase in the likelihood of positive test for SARS-CoV-2 or in the risk of severe COVID-19 [50-53]. Even if ACEI/ARBs do upregulate ACE2 receptors, the absence of upregulation of TMPRSS2 may obviate enhanced viral entry into cells [54]. These findings support current professional society guidelines recommendations to no discontinue of ACEI/ARB medications in the setting of COVID-19 pandemic [55].

COVID-19 and Cardiovascular Disease: A risk beyond of RAS inhibitors use

In COVID-19 patients, hypertension and cardiovascular disease have been identified as risk factors for adverse outcomes, without mention about how many patients were taking RAS inhibitors or any other medication [4-7]. Therefore, it is possible that a common condition beyond SRA inhibitors use is shared by these high-risk patients.

Abnormal RAS activation with increased AT-II activity plays a major role in pathogenesis and pathophysiology of hypertension, heart failure or ischemic heart disease [15,16]. On the other hand, AT-II by itself is capable to down-regulate tissue ACE-2 expression, attenuating the counter-regulatory response of tissue RAS alternate axis [56,57]. Thus, common pathophysiological status in hypertension and cardiovascular diseases may be characterized by increased AT-II activity (classical RAS axis) and decreased tissue ACE-2 expression (alternate RAS axis).

The chronic and progressive nature of cardiovascular disease, despite optimal pharmacological RAS modulation, indicates that normal balance is never reached. In other words, despite optimal treatment, cardiovascular patients are never comparable to healthy population in relation to RAS homeostasis. Interestingly, abnormal RAS activation is shared by other conditions such as aging, obesity and diabetes mellitus that are also considered risk factors for poor outcomes in COVID-19 [58-61]. Besides, pulmonary ACE-2 expression is further reduced by SARS-coronavirus infection, producing an additional tissue RAS imbalance and yielding lung injury in these patients [29].

RAS imbalance with net RAS activation, rather than RAS inhibitors use or any treatment received could be the common risk condition in these patients, rendering them more prone to poor outcomes in current pandemic. Thus, potential benefits of RAS inhibitors are reinforced and a therapeutic opportunity for this high-risk group is raised [55,61].

Finally, RAS inhibitors have proven benefits in cardiovascular diseases, and its withdrawal can precipitate serious complications or generate challenging difficulties in management among these high-risk patients [62-65]. Classical RAS inhibitors (ACEIs/ARBs) should be continuing in patients with known or suspected COVID-19 according to scientific societies’ guidelines [55].

COVID-19 and RAS: Potential therapeutic targets

Unfortunately, no vaccine or specific drug has yet approved
to treat COVID-19. Some potential RAS-related options are postulated:

- Delivering soluble forms of ACE-2: Soluble ACE-2 would serve as a decoy to virus preventing virus attachment to host cells. Additionally, soluble ACE-2 by itself can protect against lung injury by restoring pulmonary RAS balance. A pilot trial using recombinant human ACE-2 (APN01) in patients with severe COVID-19 has recently been started (ClinicalTrials.gov identifier: NCT04287686) [40, 66].

- Blocking ACE-2 receptor: Would prevent SARS-CoV-2 binding to host cells. Ideally, counter-regulatory ECA-2 activity should not be affected.

- Inhibition of membrane protease TMRSS2 activity: Priming of coronavirus S proteins by TMRSS2 protease is essential for viral entry into host cells. The serine protease inhibitor camostat mesylate, approved to treat unrelated diseases, has been shown to block TMRSS2 activity [66].

- Modulation of tissue RAS activity: Based on the pathophysiology of RAS/SARS-CoV-2 interaction, RAS modulation may have a potential role in the management of patients with pulmonary affectation by COVID-19. Paired trials of losartan as a treatment for Covid-19 are being conducted among patients who have not previously received treatment with a RAAS inhibitor and are either hospitalized (ClinicalTrials.gov identifier: NCT04312009) or not hospitalized (ClinicalTrials.gov identifier: NCT04311177) [40, 55]. Epidemiological studies are also needed to investigate clinical differences and outcomes between cardiovascular patients with COVID-19 treated and those not treated with classical RAS inhibitors.

Conclusions

Renin-angiotensin system has a pivotal role in normal physiology and pathogenesis of cardiovascular disease through dynamic balance between classical (angiotensin II mediated) and alternate (angiotensin 1-7 mediated) pathways. Angiotensin II promotes vasoconstrictive, proinflammatory and prothrombotic effects whereas angiotensin 1-7 has vasodilatory, anti-inflammatory and antithrombotic effects. RAS also seems to play a role in pathogenesis and pathophysiology of COVID-19. SARS-CoV-2 uses ACE-2 as receptor for entry into target cells and this interaction may downregulate tissue ACE-2 expression, favouring deleterious AT-II activity in lungs. Although RAS-inhibitors may increase ACE-2 expression, so far there is no data supporting that this effect facilitates viral entry or increases disease virulence. Based on current knowledge, there is no reason to withdrawal of RAS inhibitors in these patients. RAS imbalance with net RAS activation in older individuals or those with hypertension, metabolic or cardiovascular diseases could be the common risk condition that renders them more prone to poor outcomes in current pandemic. Thus, RAS modulation seems to have a potential role in the management of COVID-19. Overall, current data support potential beneficial effects of ACEI/ARB therapy in selected COVID-19 patients. Planned clinical trials are being conducted and will provide additional insight.

Competing interests

The author declares that he has no competing interests.

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