COVID-19 and RAAS inhibitors: is there a final conclusion?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), the first pandemic caused by a human infecting coronavirus, has drawn global attention from the first time it appeared in Wuhan city of China in late December 2019. Detection of the responsible viral pathogen, named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by WHO, and its possible pathogenesis lead to the forming of many hypotheses about the factors that may affect the patients’ outcome. One of the SARS-CoV-2 infection concerns was the potential role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in COVID-19 patients’ morbidity and mortality. Studies demonstrated that because SARS-CoV-2 uses human ACE2 cell receptors as an entry receptor to invade the cells, there might be an association between antihypertensive drugs such as RAAS inhibitors (specifically ACEIs and ARBs) and the COVID-19 disease. Data are scarce and conflicting regarding ACEI or ARB consumption and how it influences disease outcomes, and a single conclusion has not been reached yet.

According to the literature review in our article, the most evidentially supported theory about the use of RAAS inhibitors in COVID-19 is that these medications, including ACEI/ARB, are not associated with the increased risk of infection, disease severity, and patient prognosis. However, further studies are needed to support the hypothesis.

Keywords: COVID-19; Hypertension; Renin-angiotensin-aldosterone system inhibitors

INTRODUCTION

The Coronavirus disease 2019 pandemic has spread to almost all countries (1). The disease has first appeared in Wuhan, China, as pneumonia with an unknown origin (2-5). Researches on the bronchoalveolar lavage samples demonstrated that a new member of human coronaviruses caused pneumonia (6-8). Additional studies around the causal agent of the highly contagious pneumonia revealed the fact that SARS-CoV-2 shares almost a homological sequence with SARS-CoV and MERS-CoV (7, 9-11). Entering the human body cells, SARS-CoV-2 uses the same receptor as SARS-CoV (12, 13). Under the light of all these similarities, the main COVID-19’s pathology was predicted.

COVID-19 is known to be a principally respiratory illness with respiratory manifestations (14, 15). However, COVID-19 is currently considered a systemic infection with extrapulmonary involvement, and a broad spectrum of clinical manifestations has been found in patients with SARS-CoV-2 infection (16, 17). Notably, patients’ presentation of the disease can differ from entirely asymptomatic to severe acute respiratory syndrome and death (18).

The COVID-19 pandemic has stunned the world due to its highly contagious viral agent, multi-organ involvement, and diverse outcomes (19). As a consis-
tent feature, COVID-19 predilect to inflict adverse outcomes in patients with cardiovascular conditions or cardiovascular disease risk factors (20-23). According to the evidential data, COVID-19 tends to portend an increased severity and worse outcomes in patients with cardiovascular disease, including hypertension (20-22, 24, 25). Across the whole spectrum of cardiovascular diseases, pharmacotherapy is commonly used in patients with related conditions as it plays a significant role in the management of cardiovascular diseases (26, 27).

A wide range of pharmacological agents has objectively been shown to have beneficial effects on cardiovascular conditions, among which antihypertensive drugs, particularly RAAS inhibitors, are commonly prescribed (28). As a life-saving or life-prolonging intervention and quality of life enhancer, RAAS inhibitors have been shown to improve debilitating symptoms with approximately no side effects and the best choice for chronic pharmacological treatment in patients with cardiovascular conditions (29). Objective studies on the clinical outcomes of cardiovascular COVID-19 patients followed by a better understanding of COVID-19 pathophysiology and the prevalence of RAAS inhibitor usage among cardiovascular patients contributed to a significant hypothesis along with controversy; Is COVID-19 at any point associated with the use of RAAS inhibitors in cardiovascular patients?

COVID-19 pathophysiology

As the third member of the coronavirus family beside SARS-CoV and MERS-CoV, SARS-CoV-2 causes severe presentations (30, 31). Although COVID-19 is preferentially considered a respiratory disease with abnormal pulmonary presentations, SARS-CoV-2 infection can develop a diverse range of (various) non-respiratory manifestations, including cardiovascular abnormalities, neurological and hematological manifestations, liver damage, or kidney dysfunction symptoms (15). The systemic hyperinflammatory response induced by the virus is likely to be responsible for multi-organ involvement and extrapulmonary manifestations in COVID-19 patients (15). However, numerous studies have discussed the possibility of direct viral invasion by SARS-CoV-2 in non-respiratory organs, including the heart, relying on the presence of histopathological evidence (32-34). Autopsy analysis of 27 confirmed COVID-19 cases demonstrated that SARS-CoV-2 RNA was detectable in the heart, brain, liver, or kidneys other than the lungs (34). Similar data around the broad organotropism of SARS-CoV-2 preliminary support the possibility of direct viral attack and its role in the development of non-respiratory manifestations (32, 33).

Researches demonstrated that similar to SARS-CoV, SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor and the type 2 transmembrane serine protease (TMPRSS2) as an entry receptor for human cell invasion (35-40). However, some studies suggest that due to higher transmissibility than SARS-CoV, it is likely that SARS-CoV-2 may also use other cell surface attachment factors for entering the human cells, including sialic-acid-containing glycoproteins and gangliosides (41).

According to studies around COVID-19 pathophysiology, early in infection, SARS-CoV-2 spike (S) protein binds to the ACE2 receptor of the target cells, such as nasal and bronchial epithelial cells and pneumocytes (38). It is said that coronavirus entry into host cells is mediated by TMPRSS2, present in the host cell, promoting viral uptake by cleaving ACE2 and activating the SARS-CoV-2 spike protein (38). Similar to influenza and other respiratory viral diseases, when SARS-CoV-2 infects and kills T lymphocyte cells, a profound decrease in lymphocyte numbers (Lymphopenia) may occur in COVID-19 patients (21).

Additionally, the impaired lymphopoiesis and increased lymphocyte apoptosis subsequent to the viral inflammatory response, which is consists of an initiate and adaptive immune response, also result in decreased lymphocyte count in individuals with COVID-19 (42, 43). Furthermore, the acceleration in viral replication compromises the epithelial-endothelial barrier integrity in the later stages of the infection (44, 45). SARS-CoV-2 also accentuates the inflammatory response and triggers an influx of monocytes and neutrophils by invading pulmonary capillary endothelial cells (44, 45). Interstitial mononuclear inflammatory infiltrates and pulmonary edema filling the alveolar spaces followed by hyaline membrane formation contribute to the early phase of acute respiratory distress syndrome (ARDS) (46). Bradykinin-dependent lung angioedema and high levels of proinflammatory cytokines may also contribute to the disease (44, 45). Collectively, disruption of endothelial barrier, alveolar-capillary oxygen transmission dysfunc-
tion, and impaired oxygen diffusion capacity seems to be the main features of COVID-19 infection (47).

COVID-19 and cardiovascular comorbidities

A study by Chen et al. have demonstrated that relying on the ACE2 mRNA expression in different human organs, ACE2 receptors are highly expressed in the gastrointestinal tract, testis, and kidney (48). Although quantitative reverse transcription PCR in the lungs of 12 autopsy cases with COVID-19 detected the SARS-CoV-2 RNA at high concentrations, the lung does not seem to have the highest expression of the main receptor for the virus entry (49). Analyses show that the human heart has a higher amount of ACE2 receptor expression than the respiratory system turning it to another susceptible target organ for direct SARS-CoV-2 invasion and tissue damage (48, 49). Additionally, cardiovascular tissue damage, whether caused by a direct viral invasion or due to endothelial damage, hyperactive immune responses, and ACE2 pathways maladaptation, might contribute to cardiovascular dysfunction symptoms (50).

Cardiovascular disease (CVD) was common comorbidity in SARS or MERS patients (51-54). A considerable number of reports on clinical characteristics of confirmed cases with COVID-19 have also described similar findings (51, 54, 55). Initial reports from China demonstrated that CVD and its risk factors, particularly hypertension and diabetes mellitus, were common comorbidities among COVID-19 patients (56-60). Further evaluations showed that the prevalence of preexisting comorbidity is higher in critically ill patients (22, 57). A multicenter cohort of a total of 191 COVID-19 hospitalized patients reported the prevalence of preexisting hypertension and CVD, 30% and 24% respectively (48% of total 191 involved cases had any comorbidity) (22). Studies also declare that a hazard mortality rate exists among COVID-19 patients with preexisting hypertensive disease (61-63). Zhou et al. report a mortality rate of 3.05, with a total of 191 COVID-19 patients (22). However, it remains to be studied whether this high death ratio is associated with hypertension pathogenesis itself or to the associated comorbidity or pharmacological treatment.

The role of antihypertensive drugs

Antihypertensive drugs are used to control and manage blood pressure in patients with hypertension (64, 65). A variety of different medications are indicated in patients with hypertensive disorders, among which RAAS inhibitors including angiotensin AT1-receptor blockers (ARBs) or Renin-angiotensin system blockade with angiotensin-converting enzyme inhibitors (ACEIs) have been at the center of considerable debate (66). These medications are commonly prescribed for individuals with hypertension with high effectiveness and approximately no adverse reactions or serious complications (28). Nevertheless, the question is, “Are ACEI/ARB medications still safe and effective during the COVID-19 infection?”.

As a potential factor in the infectivity of individuals, the interaction between the virus SARS-CoV-2 and RAAS caused several concerns about the use of RAAS inhibitors and its possible correlation to the action of ACE2 and the virulence of the disease (43). As mentioned above, studies demonstrated that SARS-CoV-2 is capable of binding to ACE2 cell receptors, causing not only a direct viral invasion to cardiac and lung cells but significant deregulation of RAAS and subsequent downregulation effect of ACE2, which contributes to the accumulation of angiotensin II with proinflammatory effect (38).

Some believe that the ACE2 deactivation might have harmful effects on the development and progression of respiratory failure (43). Studies have demonstrated that the use of RAAS inhibitors, particularly ACEI and/or ARB, may increase the expression of ACE2 receptor in the respiratory tract and patient susceptibility to viral host cell entry and dissemination, leading to severe life-threatening COVID-19 complications (67-69). The use of these drugs in animal models can lead to an upregulation effect of ACE2 receptors in the myocardium and lung cells, enhancing SARS-CoV-2 virulence through facilitating the viral entry into the host cells (43, 70). Although this hypothesis is not supported with evidential data in any aspect, it resulted in the discontinuation of ACEIs/ARB’s usage prophylactically in patients with suspected COVID-19 (71).

In contrast, some researchers represent the theory of ACEI/ARB usage being beneficial in COVID-19 patients. It is suggested that since ACE2 primarily counterpoises ACE’s effect, it can act as a vasodilator, antioxidant, and anti-inflammatory, where increased (72-75). ACE2 acts to generate Ang (1-7), which leads to a vasodilatory effect that is believed
Hypertensive COVID-19 patients

Numerous studies have focused on the patients' characteristics, and have assessed the outcomes of hypertension in critically ill COVID-19 patients. In addition to these studies, some clinical trials have evaluated the potential of RAAS inhibitors for preventing hypertension in critically ill COVID-19 patients. The role of RAAS inhibitors in the management of COVID-19 patients is still under investigation. This comprehensive review discusses the current evidence on the use of RAAS inhibitors in critically ill COVID-19 patients.

| RAAS Inhibitors | Reduction in BP | Decrease in Hospitalization | Decrease in Mortality | Effectiveness |
|----------------|-----------------|-----------------------------|-----------------------|--------------|
| ACEI/ARBs      | Yes              | Yes                         | Yes                   | Good         |
| Sodium   | Reduction in BP | Yes                         | Yes                   | Good         |
| Thiazide diuretics | Reduction in BP | Yes                         | Yes                   | Good         |

Table 1. Studies with demonstrated positive association between COVID-19 and use of RAAS Inhibitors

In conclusion, RAAS inhibitors can be effective in the management of hypertension in critically ill COVID-19 patients. Further research is needed to determine the optimal use of these medications in this population.
No difference in outcomes in patients with continue or discontinue of ACE inhibitors of RAAS inhibitors of COVID-19 patients. Evidence does not suggest that RAAS blockers in the acute phase of COVID-19 may be associated with outcomes.

**Conclusion**

ACE inhibitors and ARBs in COVID-19 patients have no clinical benefit and is recommended to be continued for individuals with an indication of RAAS inhibitors (83).

Some studies have been shown in Tables 1 and 2 (83,92).

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**Table 2**

| Study Title | RAAS Blocker | n = 205 | n = 204 | p-value |
|-------------|--------------|---------|---------|---------|
| Comparison | ACE-inhibitor | 91 | 91 | 0.578 |
| RAAS | ARB | 91 | 91 | 0.668 |

**Table 3**

| Study Title | RAAS Blocker | n = 205 | n = 204 | p-value |
|-------------|--------------|---------|---------|---------|
| Comparison | ACE-inhibitor | 91 | 91 | 0.578 |
| RAAS | ARB | 91 | 91 | 0.668 |

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