ACEI/ARB drug therapy in COVID-19 patients: Yes or no?

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The recent outbreak of corona virus disease 2019 (COVID-19), caused by a new virus, has spread to most countries around the world, which is now a global pandemic and public threat.¹,² Although COVID-19 has been controlled in China, the number of new infections is still rapidly increasing in many countries and leads to a high mortality. Some studies have found that old age, as well as the comorbidities, including hypertension, diabetes mellitus, and other cardiovascular diseases, lead to a high mortality rates after infection.³,⁴ COVID-19 belongs to the same family as viruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).⁵,⁶ Generally, although the onset of patients who infected with COVID-19 is not as dangerous as those infected with SARS, and the symptoms are even mild, the disease will accelerate suddenly in the later stage after infection, even leading to multiple organ failure, which may be related to the initiation of inflammatory storm induced by imbalance of the immune response.⁷

COVID-19 AND RAAS

COVID-19 is a single-stranded RNA virus belongs to the β-group of coronavirus, which is transmitted by intermediate host or infected person through droplets.²,⁸ Previous studies revealed that COVID-19 virus penetrated into host cell, especially type 2 alveoli epithelial cells mainly through angiotensin converting enzyme 2 (ACE2) as the SARS virus.⁸,⁹ After contacting with S-protein (spike protein) of COVID-19 virus, the complete molecular structure or transmembrane region of ACE2 enters the cells together with virus through endocytosis. After penetrating into cells, the S-protein gets activated by trypsin or furin, and after the membrane fusion, viral RNA is released into the cytoplasm, and then, the virus infects the cells. Although the physiological function of ACE2 has not yet been fully elucidated, several studies have demonstrated that ACE2 is related to the virus penetrated into cells and its replication.⁵ Previous studies showed that, the expression level of ACE2 in cells is positively related with the susceptibility of S-protein of COVID-19. The expression level of ACE2 in cells was reduced significantly after COVID-19 infection, which leads to the increased level of angiotensin II (Ang II) and the activation of renin-angiotensin-aldosterone system (RAAS), thereby overactivating the Ang II type 1 receptor (AT1R) of lung cells to induce and aggravate lung injury.¹⁰,¹¹ In addition, decrease in myocardial contractility and impairing of kidney after COVID-19 infection maybe related with ACE2.¹¹,¹² Previous studies have revealed that the plasma Ang II levels of COVID-19 infections were significantly higher than those of healthy persons, and the levels of Ang II were positively correlated with virus titers and the severity of lungs injury, which showed that the infection of COVID-19 maybe induce the imbalance of RAAS of infections.¹³ In addition, some studies also demonstrated that the lungs injury after infection is caused by severe inflammatory response, also known as cytokine storm, occurred at 2–4 weeks after COVID-19.
infection, which induce the worsening of lung function, even to respiratory distress syndrome and respiratory – circulatory failure.\textsuperscript{[7, 14]} Nevertheless, the activation and maintaining of inflammatory storm is activated by the activation and overexcitation of RAAS.\textsuperscript{[15]}

**RAAS AND LUNG INJURY**

RAAS is an important endocrine system that regulates the physiological functions of the lungs and cardiovascular system and is involved in the initiation as well as progression of several diseases such as SARS, acute lung injury, hypertension, chronic kidney disease, heart failure, etc.\textsuperscript{[11, 16-18]} ACE2 and angiotensin-converting enzyme (ACE) are two important parts of RAAS and maintain the balance of function as well as structures of blood vessels. On the one hand, ACE catalyzes angiotensin I (Ang I) into Ang II, which is related to vasoconstriction, aldosterone secretion, and the vascular remodeling under pathological conditions. The main receptor of Ang II is AT1R. On another hand, ACE2 could cleave Ang I into angiotensin 1-9 (Ang 1-9), which could transform into angiotensin 1-7 (Ang 1-7) through ACE2-dependent or ACE2-independent pathways. Ang 1-7 plays an important role in the vasodilation, anti-inflammatory, anti-fibrosis and inhibits the proliferation of vessel smooth muscle cells by activation of Mas receptors.\textsuperscript{[11, 19, 20]}

Some previous studies have revealed the vital role of RAAS in acute lung injury in SARS or other influenza virus infections and showed that ACE2 associated a reduction of the pulmonary fibrosis and lungs injury caused by the overactivation of RAAS to a certain extent, which maybe related with the anti-inflammatory storm effects induced by ACE2.\textsuperscript{[10, 21]} Basu et al.\textsuperscript{[22]} also reported that the plasma ACE2 levels and Ang 1-7 in patients who suffered from hypertension combined with acute or chronic heart failure were significantly decreased and the levels of Ang II increased, while the treatment with recombinant human ACE2 could significantly induce a decline in the levels of Ang II as well as the increase in Ang 1-7 levels, which confirmed the vital role of ACE2 in the regulation of Ang 1-7/Ang II metabolic balance in the therapy of hypertension and heart and lung damage.

**ANGIOTENSIN-CONVERTING ENZYME INHIBITORS / ANGIOTENSIN RECEPTOR BLOCKERS (ACEI/ARBs) AND COVID-19**

According to the differences in clinical manifestations, imaging presentation, as well as some other complication conditions, the disease status could be grouped into four types, including mild type, with slight clinical symptoms, but no imaging presentation of pneumonia; common type, with fever, respiratory tract and other symptoms, imaging findings of pneumonia; severe type, with any of the following conditions: respiratory distress and respiratory frequency ≥30 times/min, finger oxygen saturation at rest ≤93%, oxygenation index (P\textsubscript{a}O\textsubscript{2}/F\textsubscript{I}O\textsubscript{2}) ≤300 mm Hg (1 mm Hg = 0.133 kPa), or the clinical symptoms were progressively aggravated and the lungs lesion in imaging developed >50% within 24–48 hours; critical type, with any of the following conditions: respiratory failure requires mechanical ventilation, shock, combined with organ failures need to be treated in intensive care unit.\textsuperscript{[23]} Most patients have mild or moderate symptoms after COVID-19 infection, which have the similar clinical manifestations to interstitial pneumonia.\textsuperscript{[23]} Some researchers hypothesized that for the differences in severity of COVID-19, the impact of ACEI/ARBs use on patients were differ. A referral center cohort study in Northeast of France enrolled 149 patients with severe COVID-19 showed that there was a deleterious effect of long-term therapy with ACEI/ARBs among patients with severe COVID-19 with regard to their risk of developing acute kidney injury and acute respiratory failure.\textsuperscript{[24]} However, Yang et al.\textsuperscript{[25]} found that the ACEI/ARBs treatment could result in a marginally lower death rate and less critical cases in patients with COVID-19 and hypertension, which supported the use of ACEI/ARBs in COVID-19 patients with hypertension. In addition, Di et al.\textsuperscript{[26]} found that there was no association between the use of ACEI/ARBs and COVID-19 severity or in-hospital mortality in COVID-19 patients. Zhang et al.\textsuperscript{[27]} revealed the same results with Di, showed that ACEI/ARBs therapy was not associated with a higher risk of having severe infection, but associated with a lower risk of mortality in hypertensive.

Zhang et al.\textsuperscript{[4]} have analyzed the epidemiological characteristics of COVID-19 in China and demonstrated that the infections in those who were with hypertension, diabetes mellitus, or other cardiovascular diseases and aged over 80 years old were more likely to be at highest risk of death. And, the infections in those aged over 80 years old have the highest mortality rate among all subgroups, followed by those who with cardiovascular diseases. For ACEI/ARBs are the first-line medications for blood pressure control recommended by guidelines over the world, continuous use of ACEI/ARBs in hypertensives with COVID-19 was still controversial. Several studies showed that the use of ACEI/ARBs was associated with a better prognosis, especially in hypertensives, while other studies revealed that there is no significantly correlation between ACEI/ARBs therapy and mortality of patients with COVID-19.\textsuperscript{[28-32]} Meng et al.\textsuperscript{[33]} demonstrated that ACEI/ARBs therapy could attenuate the inflammatory
response and improve the clinical outcomes of COVID-19 patients with hypertension. Zhang et al.[27] also showed continue used ACEI/ARBs in hypertensives with COVID-19 could reduce the mortality compared with those without ACEI/ARBs therapy. Furthermore, a meta-analysis demonstrated a lower mortality in hypertensives with COVID-19 with ACEI/ARBs therapy.[34] In addition, a meta-analysis enrolled 21,440 patients with pneumonia have revealed that compared with patients who were treated with placebo, the mortality reduced by 27% in those treated with ACEI, especially in Asian and post-stroke patients.[33] However, several studies in both China and some western countries found no association between the use of ACEI/ARBs and mortality of COVID-19 patients with hypertension.[30, 32, 36, 37] Studies showed that the use of ACEI/ARBs could not only alleviate the target organs damage of the underlying diseases like hypertension, diabetes mellitus, but also attenuate lungs injury by inhibiting the production or activation of Ang II.[38, 39] In addition, some studies have demonstrated that ACEI/ARBs could upregulate the expression of ACE2 mRNA and protein in some tissues in several animal models.[38] And, the use of ACEI could attenuate lungs injury by upregulating the ACE2 levels in lungs injury models.[10, 40]

Furthermore, studies have revealed that ACE2 is equivalent to natural ACEI/ARBs. The reduction of ACE2 levels would lead to lungs injury and initiate inflammatory storm by making the balance of RAAS to ACE/Ang II/AT1R axis, while the increase of ACE2 levels would play a protective effects on cardiopulmonary by making the balance to Ang 1-7/Mas axis.[10, 41] Thus, whether it is the activation of ACE2 or the upregulation of ACE2 caused by the intake of ACEI/ARBs drugs, it may perform an anti-inflammatory protection effect against lung injury caused by COVID-19.

BRACE-CORONA study, the latest clinical trials published in ESC 2020 on September 01, 2020, has showed that the proportion of survived and discharged from hospital was 91.8% and 95%, respectively, in COVID-19 patients who discontinued the use of ACEI/ARBs drugs and those continued the use of ACEI/ARBs treatment, and the mean survival days as well as days of discharge are 25 days in both groups, which revealed that the use of ACEI/ARBs drugs has no effect on the survival rate of COVID-19 infections.[42, 43]

COVID-19 is now a major challenge to the global public health. Although the vaccines against COVID-19 undergoing clinical trials have been proved effective, the epidemiological characteristics, pathogenicity of virus, and the pathophysiological changes after infection were still unclear. And, further study to investigate specific clinical treatments is urgently needed. Whether the use of ACEI/ARBs in COVID-19 infection would aggravate the risk of death remains controversial. All in all, in patients with hypertension or other cardiovascular diseases who could effectively control blood pressure or reduce the incidence of complication by taking ACEI/ARBs drugs should continue the ACEI/ARBs treatment. Sudden discontinuation or dressing change will inevitably increase other risks. Strengthen family self-monitoring of blood pressure, and continuing the ACEI/ARBs treatment under the guidance of physicians is the best choice under COVID-19 threat.

Conflict of Interest

The authors declared no conflicts of interest.

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