



Antihypertensive treatment with ACEI/ARB of patients with COVID-19 complicated by hypertension

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Currently, the novel coronavirus (COVID-19) has spread to many countries around the world. Due to the increasing number of confirmed cases and public hazards, COVID-19 has become a public health emergency of international concern and has received much attention from health organizations worldwide.

At present, the pathogenesis of COVID-19 has not been elucidated [1]. However, a preliminary study speculated that it might enter the human body via angiotensin-converting enzyme 2 (ACE2) on the surfaces of type II alveolar cells [2]. Analysis of the clinical characteristics of patients with COVID-19 suggested that patients with hypertension comprised 20–30% of all patients and up to 58.3% of patients in the intensive care unit and have been responsible for 60.9% of deaths caused by COVID-19. The renin-angiotensin system (RAS) plays an important role in the occurrence and development of hypertension, and ACE inhibitors (ACEIs) and angiotensin receptor antagonists (ARBs) are the main antihypertensive drugs recommended by the current guidelines. Therefore, what should be done in regard to ACEI/ARB for the antihypertensive treatment of patients with COVID-19 complicated by hypertension? We will conduct a specific analysis as follows.

Relationship between ACE2 and COVID-19

A study has revealed that the spikes of COVID-19 could bind to the surface receptors of sensitive cells after

contacting the airway surface, which may mediate virus entry into target cells and viral replication, and ACE2 might be a mediator of infection [3]. The binding of COVID-19 to ACE2 is not as strong as that of SARS-associated coronavirus (SARS-CoV) to ACE2, but it is still much higher than the threshold required for virus infection [3]. Another study found that COVID-19 must bind to ACE2 to enter HeLa cells [4]. Several key residues, especially Gln493, of the COVID-19 receptor-binding motif have close interactions with human ACE2 [5]. The virus may exhibit pathogenic activity by attacking type II alveolar epithelial cells expressing ACE2. Previous studies of coronaviruses that cause severe acute respiratory syndrome (SARS) have revealed that they bind to ACE2 in alveoli pulmonis through their surface spike proteins and then cause lung damage and even lung function failure. ACE2 is likely to be the cellular receptor of COVID-19, but whether it is the only cellular receptor remains to be further investigated.

Biological characteristics of ACE2 and ACE

ACE and ACE2 are widely distributed in the human body; the former is mainly found in lung, kidney, heart, and blood vessel tissue, while the latter is more abundant in the digestive tract, lung, kidney, heart, and blood vessels. Strictly speaking, ACE2 is not an isozyme of ACE but a homologous enzyme [6]. It was initially thought that ACE2 was distributed only in the heart, kidney, and testis [7], but it has recently been found that ACE2 is also expressed in lung, liver, spleen, brain, intestine, placenta, heart and many other tissues, and its tissue distribution is organ specific; it is highly expressed in the kidney and cardiovascular and gastrointestinal systems, while its expression level is low in lung, the central nervous system and lymphoid tissue [8–10]. In the RAS, renin hydrolyzes angiotensin into angiotensin I (Ang I), which is subsequently converted by ACE to Ang II, and Ang II binds to angiotensin receptor 1 (AT1R) on the vascular smooth muscle cell membrane, which causes a variety of effects, including vasoconstriction

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and vascular remodeling. ACE2 could hydrolyze Ang I into inactive Ang1–9 and hydrolyze Ang II into Ang1–7. Ang1–7 could act on the Mas receptor to play a role in cardiovascular protection, including vasodilation, anti-proliferation, and antioxidative stress. Therefore, this reveals that, *in vivo*, the ACE-Ang II-AT1R axis and the ACE2-Ang1–7-MAS axis function as checks and balances to maintain homeostasis.

Expression of ACE2 in human lung tissue

In normal human lung tissues, ACE2 is expressed in type I and II alveolar epithelial cells [11, 12]. Some studies have analyzed the expression profiles of ACE2 RNA in normal human lung and showed that the expression of the viral receptor ACE2 is concentrated in a small number of type II alveolar (AT2) cells. More importantly, these AT2 cells not only express viral receptors but also express more than 20 other genes closely related to virus replication and transmission, which indicates that AT2 cells are likely to be the target cells of COVID-19. It was found that 0.64% of human lung cells expressed ACE2, and more than 80% of total ACE2 expression was found in AT2 cells by comparing data from 43134 single-cell RNA sequencing results from normal lung tissues from eight different racial/ethnic groups. Surprisingly, the proportion of ACE2-positive cells was 2.5% in the only Asian (male) specimen, which was much higher than that in the African and white (only 0.47%) specimens, which suggested that Asian populations might be more susceptible to COVID-19 [13]. In addition, the percentage of cells expressing ACE2 was higher in men than in women [13], but the sample size was smaller (just eight cases), and larger-scale sample data are needed to further confirm this conclusion. High expression of ACE2 in AT2 cells can explain the severe alveolar injury phenomenon observed after COVID-19 infection and provide a reference for the formulation of a new coronavirus pneumonia treatment strategy in the future.

Effects of RAS inhibitors on ACE2

An early study showed that ACE2 shows 42% homology with ACE [6], but the substrate specificity and enzymatic activity of the two enzymes are quite different. The main substrate of ACE is Ang I, which can be blocked by ACEI. The physiological effect of increased Ang I levels *in vivo* is mainly characterized by vasoconstriction, while ACE2 hydrolyzes Ang I into Ang1–9, which is subsequently transformed into Ang1–7 by ACE. These proteins mainly show protective effects, such as vasodilatory, anti-inflammatory, endothelial protective, anti-cell proliferative, anti-hypertrophy, and anti-fibrosis effects. However, after ARB

treatment, the levels of Ang I and Ang II, as ACE2 substrates, were significantly increased, which could induce ACE2 expression and increase its activity in generating Ang1–7 and thus contribute to significant cardiac, cerebral, renal, and vascular protective effects. Under normal conditions, ACE2 and ACE show vasodilator and vasoconstrictor functions, which jointly maintain the homeostasis of blood pressure. Many previous studies have confirmed that the activity of ACE2 may increase after the use of RAS inhibitors, which may be beneficial for the control of blood pressure [14]. Currently, it is known that the effect of RAS inhibitors on ACE2 is mainly due to the expression of ACE2 in the heart, kidney and plasma, and it is not fully understood whether RAS inhibitors can influence the expression of ACE2 in airway epithelial cells. In addition, the expression of ACE2 may be lower in patients with hypertension than in people with normal blood pressure. To date, there is no evidence that using RAS inhibitors makes patients more susceptible to the virus. However, another study showed that treatment with an ACEI or ARB may downregulate the expression of ACE2 but have no significant effect on its activity [14].

Is there a correlation between ACE2 gene expression and enzyme activity?

Animal studies showed that cardiac ACE2 mRNA expression levels increased after treatment with lisinopril alone, but ACE2 activity did not increase correspondingly, while cardiac ACE2 mRNA expression levels and activity increased after treatment with losartan alone. After further combined treatment with losartan and lisinopril, there was no significant change in ACE2 activity compared to that observed with treatment with losartan alone, and it offset the effect of losartan on increasing the expression of ACE2 mRNA. Therefore, there is a lack of correlation between the rise and fall of cardiac ACE2 mRNA expression and its activity. These results indicated that angiotensin might be involved in a more complex signal conduction mechanism by which an ACEI/angiotensin II receptor antagonist (ARB) may regulate the gene expression and activity of ACE2 [14].

Are ACE2 expression levels correlated with the severity of viral infection?

A recent study revealed that SARS-CoV was not isolated from patients with high expression of ACE2, which suggested that the viral infection process may require other receptors or cofactors [13]. In addition, further studies are needed to clarify whether hypertensive drugs alter the gene expression and activity of ACE2 in human lung tissues, thus affecting the disease outcome of novel coronavirus pneumonia.

Conclusion

In conclusion, although there is no conclusion regarding the association of COVID-19 with RAS inhibitors, RAS inhibitors can affect the expression of ACE2 mRNA and the activity of ACE2 in tissues; theoretically, it is possible that ACE2 could promote the proliferation of COVID-19 and enhance its capability for infection. Therefore, large-scale clinical studies are urgently needed to explore COVID-19 susceptibility and corresponding treatment strategies in patients with hypertension treated with RAS inhibitors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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