VIEWPOINTS

Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

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The prevalence of coronavirus disease 2019 (COVID-19) has posed a great threat to people's health worldwide, bringing a great challenges to the public healthcare systems. A recent study has confirmed that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) uses severe acute respiratory syndrome coronavirus (SARS-CoV) receptor angiotensin-converting enzyme 2 (ACE2) for host cell entry.[1] ACE2 expression was previously found to correlate with susceptibility to SARS-CoV infection in vitro.[2] As with SARS-CoV, higher ACE2 expression might also lead to higher risk of SARS-CoV-2 infection.

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According to available clinical data, ≈15% to 30% of the COVID-19 patients are with hypertension and ≈2.5% to 15% are with coronary heart disease.[3–5] Angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are widely used in the treatment of these cardiovascular diseases. Interestingly, several studies have shown that ACEIs/ARBs exhibit ability to upregulate ACE2 expression in addition to their main pharmacological effect to inhibit angiotensin-converting enzyme 1 (ACE1) or block angiotensin II type 1 receptor.[6–8] Considering that ACE2 expression might correlate with the susceptibility to SARS-CoV-2, intake of ACEIs/ARBs might predispose patients to the infection of SARS-CoV-2. Therefore, some cardiologists suggested that patients should discontinue ACEIs/ARBs to avoid the potential increased risk of SARS-CoV-2 infection.[9]

However, there is evidence demonstrating that the activation of the renin-angiotensin system (RAS) and the downregulation of ACE2 expression are involved in the pathological process of lung injury after SARS-CoV infection.[10] Recently, it has been reported that serum level of angiotensin II is significantly elevated in COVID-19 patients and exhibits a linear positive correlation to viral load and lung injury.[11] Activation of the RAS can cause widespread endothelial dysfunction and varying degrees of multiple organ (heart, kidney, and lung) injuries. Thus, intake of ACEIs/ARBs might probably relieve

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the lung injury and absolutely decrease heart and renal damage resulting from the RAS activation.

These possibilities pose a dilemma for the cardiologists in terms of recommending whether to discontinue ACEIs/ARBs or not. On the basis of the current literature, a viewpoint on the potential influence of ACEIs/ARBs on the onset and severity of SARS-CoV-2 infection is proposed in this article.

ROLE OF ACE2 IN THE CARDIOVASCULAR SYSTEM

ACE2 was first discovered as a homologue of ACE1 in 2000, which converts angiotensin II to angiotensin 1-7. ACE2 is a type I transmembrane protein, which is mainly anchored at the apical surface of the cell. Its catalytic domain is located at the extracellular side of the cell, which can be cleaved and released into blood by ADAM17 (a disintegrin and metalloproteinase domain-containing protein 17).[12] The recombinant human ACE2 (rhACE2), which is purified from the supernatant of ACE2 transfected cells, can generate angiotensin 1-7 from angiotensin II and shows the ability to prevent angiotensin II–induced myocardial hypertrophy, diastolic dysfunction, and myocardial fibrosis.[12] But the role of cleaved ACE2 in circulation is still unclear.

ACE2/angiotensin 1-7 axis is another arm of RAS, which generally shows the opposite effect to the ACE1/angiotensin II axis.[12] While angiotensin II can induce strong vasoconstriction, proinflammatory effects, and profibrotic effects, angiotensin 1-7 exhibits antiproliferative, antiapoptotic, and mild vasodilating abilities and presents various cardiovascular protective effects, including anti–heart failure, antithrombosis, anti–myocardial hypertrophy, antifibrosis, antiarrhythmia, anti-atherogensis, and attenuating vascular dysfunction related to metabolic syndrome.

The disruption of the subtle balance between ACE1 and ACE2 can lead to the dysregulation of blood pressure. ACE2 is widely expressed in cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells, which are also a regulator for heart function. Studies have found that overexpression of ACE2 can prevent or even reverse the heart failure phenotype, whereas loss of ACE2 can accelerate the progression of heart failure. The activity of circulating ACE2 in patients with heart failure is also significantly higher than in normal people, which is associated with poor prognosis. Shedding of the membrane-bound ACE2 may be responsible for the increased circulating ACE2 activity in patients with heart failure.

ROLE OF ACE2 IN COVID-19

SARS-CoV-2, as its name indicates, shares many similarities with SARS-CoV. SARS-CoV-2 uses the SARS-CoV receptor ACE2 for host cell entry.[1] Although ACE2 expression correlates with susceptibility to SARS-CoV infection in vitro,[2] the relationship between ACE2 expression level and the susceptibly of SARS-CoV-2 infection remains unclear. Li et al[13] retrospectively analyzed 425 confirmed cases of COVID-19 and found that few cases occurred in children. There is a possibility that it might be attributable to the difference in expression of ACE2 between children and adults. However, there is a lack of evidence to show that ACE2 expression varies with age. Only one study has analyzed the age-dependent differences in pulmonary host responses in acute respiratory distress syndrome (ARDS), and the authors found that there is no difference in activity of ACE2 in bronchoalveolar lavage fluid from neonates, children, adults, and older adults with ARDS.[14] Another concern is that the higher ACE2 level might be associated with a higher local viral load. The differential pseudotype SARS-CoV-2 entry among different kinds of cells has been provided in detail in a recent study,[1] and the relative expression level of ACE2 mRNA of some of the tested cells could be found in the Cancer Cell Line Encyclopedia database. We found that the expression of ACE2 was relatively higher in cells with higher pseudotype SARS-CoV-2 entry, according to the Cancer Cell Line Encyclopedia database. It has been reported that higher initial viral load was associated with worse prognosis in SARS.[15] A similar situation might also exist in COVID-19. However, no direct evidence has indicated a connection between ACE2 expression and the susceptibility and severity of SARS-CoV-2 infection.

It has been reported that 3% to 20% of COVID-19 patients are combined with ARDS.[3–5] Recent studies have found that the RAS activation plays an important role in acute lung injury.[16] ARDS animals showed reduced ACE2 activity, and loss of ACE2 can cause exaggerated neutrophil accumulation, enhanced vascular permeability, and exacerbated pulmonary edema, which eventually lead to ARDS. Supplement of exogenous ACE2 can attenuate the inflammatory response and increase oxygenation in various ARDS animal models.[16] A phase 2 double-blind multicenter clinical trial of rhACE2, GSK2586881, in ARDS was conducted by Khan et al in 2017.[17] It turned out that serum angiotensin II was higher in nonsurvivors than in survivors, whereas GSK2586881 significantly decreased angiotensin II level and interleukin-6 concentration. In addition, the concentration of SP-D (surfactant protein D), which is generally an anti-inflammation and antimicrobial protein, also increased after GSK2586881 infusion.

Interestingly, Kuba et al found that the expression of ACE2 in lung tissues was significantly downregulated in mice after SARS-CoV infection, accompanied with the increased pulmonary vascular permeability and the pulmonary edema.[10] They also discovered that injection

of the SARS-CoV Spike protein alone could decrease lung ACE2 expression and cause acute lung injury, which can be alleviated by ACEIs/ARBs. Considering that the configuration of Spike protein of SARS-CoV and SARS-CoV-2 is almost the same, SARS-CoV-2 infection might also downregulate the ACE2 expression in the lung, which might take part in the pathological process of the lung injury.

POTENTIAL HEART INJURY IN COVID-19

As with SARS, patients with COVID-19 also showed potential cardiac injuries. Chen et al reported that among the 99 confirmed COVID-19 patients admitted to Wuhan Jinyintan Hospital, 13 (13%) presented elevated creatine kinase and 75 (76%) showed the elevation of lactate dehydrogenase.[3] Wang et al described the clinical characteristics of 138 hospitalized COVID-19 patients at Zhongnan Hospital of Wuhan University and found elevated hypersensitive troponin I in 10 (7.2%), whereas 23 (16.7%) had arrhythmia.[4] Besides, Guan et al extracted the data on 1099 COVID-19 patients from 552 hospitals in 31 provinces/provincial municipalities and found that 90 of 675 (13.7%) were with an elevated creatinine kinase level and 277 of 675 (37.2%) showed an increased lactate dehydrogenase level.[5] The myocardial dysfunction can be indirect, caused by reduced oxygen supply, severe lung failure, and the cytokine storm after the SARS-CoV-2 infection. However, there is also the possibility that it might be attributable to the decreased activity of ACE2 in the heart, just like SARS. Oudit et al[18] detected the presence of SARS-CoV and a marked decreased ACE2 expression in the heart of intranasal SARS-CoV–infected mice. They also reported that SARS-CoV was isolated from 7 of 20 of the human autopsy hearts, and the myocardial damage was accompanied by the decreased protein expression of myocardial ACE2 as well. Recently, an autopsy case of COVID-19 was reported in Chinese.[19] Liu et al[19] observed a moderate amount of transparent light-yellow liquid in the pericardial cavity and mild epicardial edema in an 85-year-old man who died from COVID-19. They also reported that the myocardial section was gray-red fish-like. Considering that this old patient showed a history of coronary heart disease, whether the myocardial injury was associated with SARS-CoV-2 infection is still unclear. However, direct evidence demonstrating that SARS-CoV-2 infects the heart and decreases the ACE2 expression is currently lacking.

ACEIS/ARBS AND ACE2

Several studies have shown that ACEIs/ARBs exhibit ability to upregulate ACE2 expression in addition to their main pharmacological effect to inhibit ACE1 or block the angiotensin II type 1 receptor. Enalapril can restore left ventricular ACE2 expression levels in rats with heart failure.[7] Losartan and olmesartan can increase the expression of ACE2 mRNA in the heart of rats after myocardial infarction.[8] It was found that lisinopril can increase the level of ACE2 mRNA but not the activity of ACE2 in the heart of normal Lewis rats, whereas losartan can simultaneously increase the mRNA expression as well as the protein activity of ACE2 in the heart of Lewis rats.[6] However, the current research is mainly limited to the effects of ACEIs/ARBs on the changes of ACE2 mRNA levels and activity in animal hearts. The effects of ACEIs/ARBs on ACE2 mRNA levels and protein activity in human lung tissues are still unclear.

ACEIS/ARBS MIGHT PLAY A DUAL ROLE IN COVID-19

To sum up, the evidence at present shows that ACEIs/ARBs could increase the expression and activity of ACE2 in heart, performing the protective role in cardiovascular system. However, the impact of ACEIs/ARBs on ACE2 in other organs, especially whether they could influence the expression level and activity of ACE2 in lungs, remains unknown. If ACEIs/ARBs do own the ability to upregulate the expression and activity of ACE2 in lungs, they may play a dual role in COVID-19. On the one hand, the higher level of ACE2 might increase the susceptibility of cells to SARS-CoV-2. On the other hand, the activation of ACE2 might ameliorate the acute lung injury induced by SARS-CoV-2.

We now return to our initial question: should we discontinue ACEIs/ARBs for patients who have been taking them for a long time in the context of COVID-19? The authors believe that the answer might be no. The use of ACEIs/ARBs might be a double-edged sword in COVID-19. On the one hand, it might lead to an increased risk of SARS-CoV-2 infection. On the other hand, it might reduce the severity of lung damage caused by the infection. However, it would be unwise to discontinue these medications assertively because the protective role of ACE2 in the respiratory system is supported by ample evidence, whereas the increased danger of infection is still a hypothesis. Besides, patients with COVID-19 also showed potential cardiac injuries and the RAS activation. As shown in the Figure, the SARS-CoV-2 infection could possibly influence the balance between angiotensin II and angiotensin 1-7, whereas ACEIs/ARBs can block the RAS and protect the heart and other organs, which are susceptible to injury caused by the RAS activation.

RHACE2 WITH AN FC FRAGMENT MIGHT BE A PROMISING DRUG CANDIDATE FOR THE TREATMENT OF COVID-19

As we have discussed above, reducing the expression of ACE2 may not be the best way to prevent COVID-19. On the contrary, blocking the interaction of virus with its cellular receptor by soluble virus receptor analogs is generally a promising approach for treatment of viral infection. Exogenous supplement of rhACE2 might be a brilliant idea in the treatment of COVID-19, especially for those patients with cardiovascular diseases. On the one hand, researchers already found that injecting exogenous rhACE2 protein could relieve lung injuries in several acute pneumonia experimental models and also show the ability to prevent angiotensin II–induced hypertension, myocardial hypertrophy, diastolic dysfunction, and myocardial fibrosis. On the other hand, soluble ACE2 may act as the bait to neutralize the Spike protein on the surface of the SARS-CoV-2, thus inhibiting the invasion of viruses. In fact, a recent study has demonstrated that fusion protein of rhACE2 with an Fc fragment shows high affinity binding to the receptor-binding domain of SARS-CoV-2 and potently neutralized SARS-CoV-2 in vitro,[20] which provides a basis for further drug development. In this study, Lei et al[20] constructed 2 fusion proteins, ACE2-Ig and mACE2-Ig, by connecting the extracellular domain of human ACE2 or an ACE2 variant to the Fc domain of human IgG1, separately. They reported a stable pharmacokinetic property for both proteins after intravenous administration in mice. By using viruses pseudotyped with the Spike protein of SARS-CoV and SARS-CoV-2, they found that both SARS-CoV and SARS-CoV-2 can be neutralized by the fusion proteins in vitro.

Without a doubt, in clinical practice, physicians are faced with much more complicated situations, calling for more evidence from laboratory and clinical research. Herein, we provide several potential directions for future research. For example, the effect of exogenous supplement of rhACE2 with an Fc fragment on the susceptibility and severity of COVID-19 needs to be further investigated.
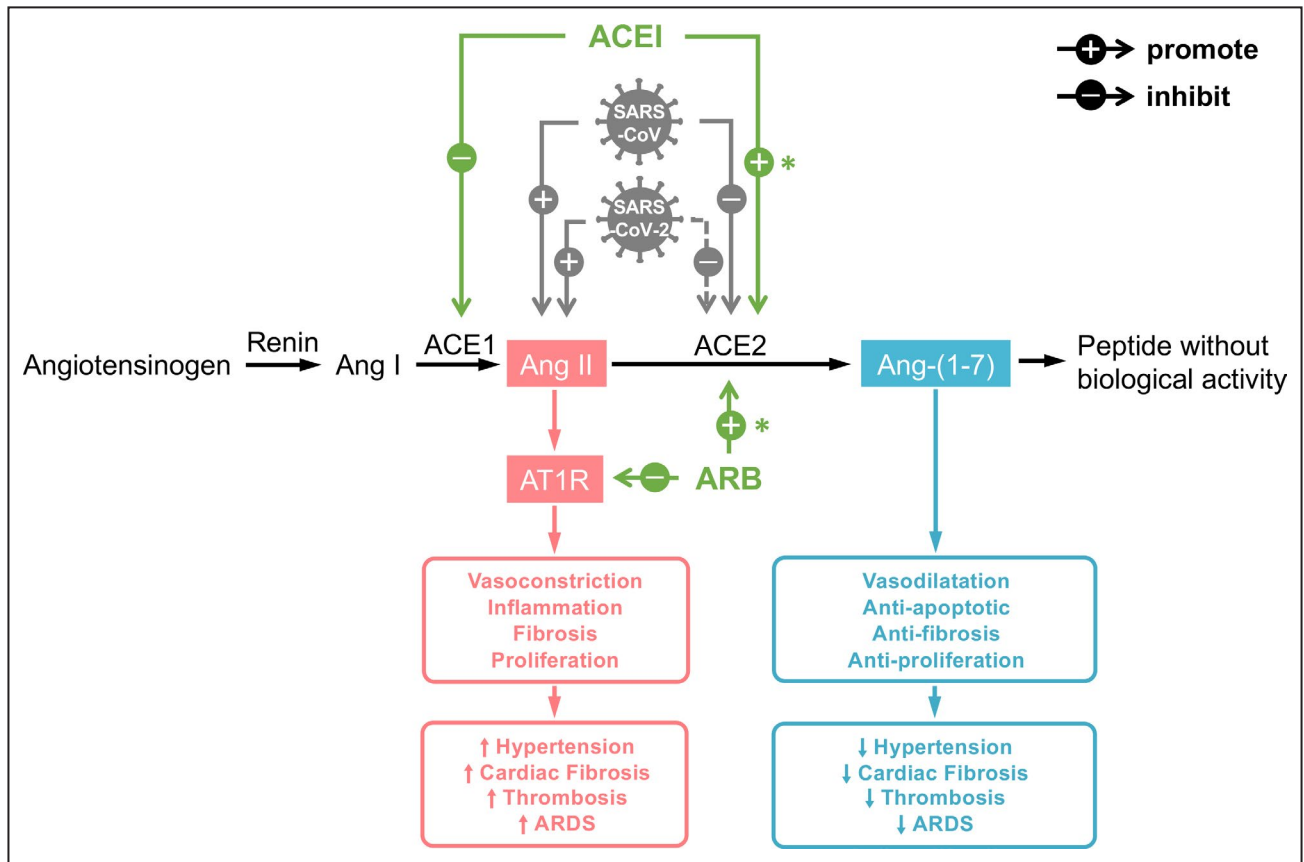

Figure. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/severe acute respiratory syndrome coronavirus (SARS-CoV) infection could possibly influence the balance between angiotensin II (Ang II) and angiotensin 1-7 (Ang-[1-7]).
*indicates finding in hearts; ACE1, angiotensin-converting enzyme 1; ACE2, angiotensin-converting enzyme 2; ACEI, angiotensin-converting enzyme inhibitor; Ang I, angiotensin I; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; AT1R, angiotensin II type 1 receptor; dotted line, speculation based on the current evidence; solid line, findings from current evidence; up arrow, promote; down arrow, inhibit.

Besides, we should address the importance of autopsy of COVID-19 patients to confirm the damage caused by SARS-CoV-2 and the change in ACE2 expression level in both lung and heart after SARS-CoV-2 infection. In addition, we could explore the effects of ACEIs/ARBs on the expression of ACE2 in other organs, especially the lung, through animal experiments to verify the role of ACEIs/ARBs in acute lung injury models. Most important, a retrospective analysis of existing clinical data can be performed to compare the severity of pulmonary inflammation and heart injury between COVID-19 patients taking ACEIs/ARBs and other cardiovascular drugs.

Taken together, ACE2 plays a protective role in both cardiovascular diseases and acute lung injury. For uninfected patients, we tend to believe it is unnecessary to discontinue ACEIs/ARBs given the lack of evidence to support the hypothesis that ACEIs/ARBs might lead to an increased risk of SARS-CoV-2 infection. For infected patients, although higher ACE2 expression might be associated with higher viral loads, ACEIs/ARBs should not be discontinued assertively because they can block the RAS and protect patients from the potential heart injuries in COVID-19 and might also reduce the severity of lung damage caused by the infection. However, there is no immediate need to initiate ACEIs/ARBs because there has been no definite evidence that they benefit COVID-19 patients' survival. Exogenous supplement of rhACE2 may be a good way to prevent and treat COVID-19. More evidence from laboratory and clinical research is needed for further progress in the treatment of COVID-19.

ARTICLE INFORMATION

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Disclosures
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