



# Inhibitors of the renin–angiotensin system: The potential role in the pathogenesis of COVID-19

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## Abstract

*Coronavirus disease 2019 (COVID-19), which initially began in China, has spread to other countries of Asia, Europe, America, Africa and Oceania, with the number of confirmed cases and suspected cases increasing each day. According to recently published research, it was found that the majority of the severe cases were elderly, and many of them had at least one chronic disease, especially cardiovascular diseases. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) are the most widely used drugs for cardiovascular diseases. The clinical effect of ACEIs/ARBs on patients with COVID-19 is still uncertain. This paper describes their potential role in the pathogenesis of COVID-19, which may provide useful in the advice of cardiologists and physicians. (Cardiol J 2020; 27, 2: xx–xx)*

**Key words:** COVID-19, 2019-nCoV, renin–angiotensin system, angiotensin-converting enzyme inhibitors

## Introduction

Since December 2019, a series of pneumonia cases of unknown etiology were reported in Wuhan, Hubei province, China. A novel coronavirus named 2019 novel coronavirus (2019-nCoV) was identified by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient and the disease was subsequently officially named COVID-19 by the World Health Organization. As of March 20, 2020, more than 240,000 people have been confirmed with COVID-19 across the world. A pandemic of the novel coronavirus has posed significant threats to international health and the economy [1, 2].

2019-nCoV is the seventh coronavirus that has been confirmed to infect humans. It has 50% genomic similarity to the Middle East respiratory syndrome coronavirus (MERS-CoV), 75–80% to the severe acute respiratory syndrome coronavi-

rus (SARS-CoV) and 96% to a coronavirus found in bats. 2019-nCoV encodes at least 27 proteins, including 15 non-structural proteins, 4 structural proteins, and 8 auxiliary proteins. Spike glycoprotein (S) which locates on the outer envelope of the virion is responsible for binding to the host receptor angiotensin-converting enzyme 2 (ACE2).

The majority of the severe patients diagnosed with COVID-19 were elderly. In a study of 52 severe, adult patients, researchers found that the mean age of these patients was 60 years and 40% of these patients had at least one chronic disease such as hypertension [3, 4]. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), which are the most widely used drugs for hypertension. But whether ACEIs/ARBs should be used in patients with COVID-19 is still a question worthy of discussion. This paper describes its potential role in the pathogenesis of COVID-19, which may provide useful advice for cardiologists and physicians.

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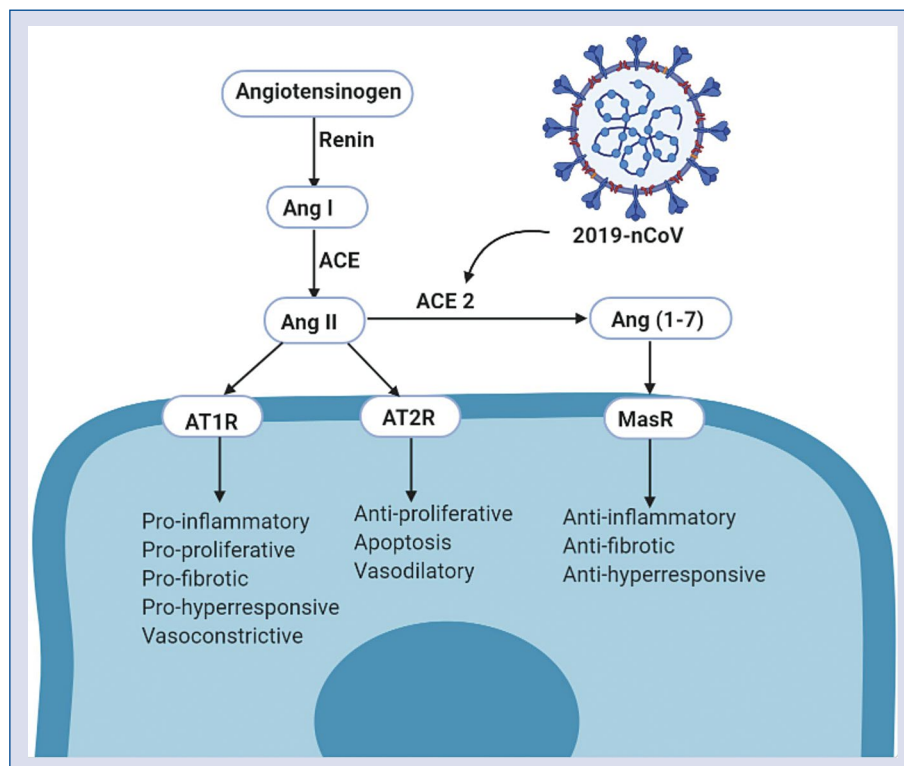


Figure 1. The renin–angiotensin system and 2019-nCoV.

### Renin–angiotensin system and multi-system inflammation

Renin, a protease that is generated primarily in the kidney, cleaves angiotensinogen to generate angiotensin I (AngI). Subsequently, a protease called angiotensin-converting enzyme (ACE) cleaves AngI to produce angiotensin II (AngII). AngII is a key effector of the renin–angiotensin system (RAS) and exerts biological functions through two receptors: AngII receptor type 1 (AT<sub>1</sub>R) and AngII receptor type 2 (AT<sub>2</sub>R). AT<sub>1</sub>R is coupled to G protein-coupled receptor which can stimulate multiple signaling pathways including tyrosine kinases, MAPK/ERK, Rho/ROCK kinase and PLCβ/IP3/diacylglycerol. AT<sub>1</sub>R activation mediates catecholamine release from peripheral sympathetic neurons, inflammation via NF-κB activation, ROS production through NADH/NADPH oxidase activity, apoptosis via toll-like receptor 4 activation and lung fibroblast proliferation. ACE2, a homologue of ACE, is responsible for producing Ang(1–7) by cleaving AngII. Ang(1–7) binds and activates G protein-coupled Mas receptor to exert anti-inflammatory and anti-remodeling effects [5–7]. ACE2 is abundantly present in the epithelia

of the lung and small intestine. It was also present in most arterial and venous endothelial cells and arterial smooth muscle cells [8–10]. In a study published recently, researchers found that the distribution of ACE2 is more widespread in males than in females: at least 5 different types of cells in the male lung express this receptor, while only 2~4 types of cells in female lungs express the receptor. The ACE2/Ang(1–7)/Mas receptor pathway often serves to counter-regulate the pro-inflammatory, pro-fibrotic and pro-hyperresponsive effects of the ACE/AngII/AT<sub>1</sub> receptor pathway. The imbalance between ACE/AngII/AT<sub>1</sub> receptor pathway and ACE2/Ang(1–7)/Mas receptor pathway in the RAS will lead to multi-system inflammation (Fig. 1). And increased ACE and AngII are poor prognostic factors for severe pneumonia [11, 12].

Activation of the ACE2/Ang(1–7)/Mas receptor pathway is also proven to play a possible role in cardio-protection. Ferreira firstly put forward that low concentrations of ANG-(1–7) produced a significant reduction of ischemia/reperfusion induced cardiac arrhythmias in isolated rat hearts. In addition to influencing cardiac rhythm, ANG-(1–7) has a significant anti-remodeling effect in different models of cardiomyopathy. It may be concluded that

an increased level of ANG-(1–7) may prevent heart dysfunction, inhibit oxidative stress, protect against cardiac hypertrophy, and attenuate left ventricular remodeling. Not only in the respiratory and cardiovascular system, but also anti-inflammatory effects of ACE2/Ang(1–7)/Mas receptor pathway in kidney, liver, central nervous system, endocrine system, and others have also been successively confirmed [13].

### **Renin-angiotensin system and COVID-19**

2019-nCoV infects people via the Spike-ACE2 binding pathway [14, 15]. The binding of 2019-nCoV and ACE2 resulted in the exhaustion of ACE2 and then ACE2/Ang(1–7)/Mas receptor pathway was inhibited. The inhibition of this system may lead to many pathophysiological changes. In an animal trial published in “Nature”, it showed that loss of ACE2 expression precipitated severe lung injury. They also performed a rescue experiment by using recombinant human ACE2 protein (rhuACE2). The results showed that injection of rhuACE2 into acid-treated ACE2 knockout mice decreased the degree of acute lung injury which is assessed by lung elastance and pulmonary edema formation. When they injected rhuACE2 protein into acid-treated wild-type mice, lung function and edema formation were also rescued [16–18].

Of note, demonstrated herein, was that serum AngII level were extremely elevated in COVID-19 patients. More importantly, plasma AngII levels were linked to disease severity and predicted a fatal outcome in these patients. To test whether Spike-Fc injections indeed affect the function of the RAS, researchers analyzed AngII levels in the lungs of Spike-Fc-treated mice. Notably, a significant increase was observed in AngII levels in the lung tissue of these mice. To further confirm whether Spike-Fc promotes lung disease pathogenesis through increased AngII, they blocked the AT<sub>1</sub>R with a specific inhibitor. The results showed that inhibition of the AT<sub>1</sub>R indeed attenuated acute severe lung injury and pulmonary edema in these mice [19, 20]. Taken together, it is concluded that 2019-nCoV can exaggerate acute lung failure through deregulation of the ACE/AngII/AT<sub>1</sub> receptor pathway. Moreover, 2019-nCoV Spike-mediated lung failure can be rescued by the inhibition of AT<sub>1</sub>R.

### **ACEIs/ARBs and COVID-19**

According to the reasons described below, it may speculated that ACEIs/ARBs could be used in

patients with COVID-19 to reduce the multi-system inflammation response and mortality by decreasing AngII level. But some researchers have proposed a different point of view. What is known is that 2019-nCoV infects patients by the binding receptor ACE2. Use of ACEIs/ARBs may contribute to an increased level of ACE2 which makes the virus more likely to invade cells [21, 22]. Some scientists have suggested using ACE2 inhibitor called N-(2-aminoethyl)-1 aziridine-ethanamine to block the 2019-nCoV spike protein-mediated cell fusion [23].

ACEIs/ARBs reduces the multi-system inflammation response in patients with COVID-19. But it also provides the virus with more receptors. The clinical effect it brings needs prospective studies and clinical trials to confirm this. Some scientists have suggested that the most rapid approach for assessing its feasibility is to analyze clinical patient records to determine whether COVID-19 patients who were medicated with AT<sub>1</sub>R antagonists prior to their diagnosis had better disease outcome. If COVID-19 patients medicated with AT<sub>1</sub>R antagonists have reduced pulmonary inflammatory response and lower mortality, this would support the notion that ACEIs/ARBs confer protection from severe symptoms among 2019-nCoV infected individuals. Knowledge gained from such datamining of clinical records may prove that ACEIs/ARBs provides positive clinical effect evidence for COVID-19 patients [24].

### **Conclusions**

ACEIs/ARBs might be an attractive therapeutic agent to treat COVID-19 patients with cardiovascular diseases by reducing the pulmonary inflammatory response. The fact that increased levels of ACE2 may provide 2019-nCoV with more receptors and make it easier to invade cells should not be ignored. More prospective studies and randomized clinical trials are needed to prove its clinical effect on COVID-19 patients.

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