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COMMENTARY

The concern about ACE/ARB and COVID-19: Time to hold your horses!

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ABSTRACT

Concern about coronavirus 2019 (COVID-19) morbidity and mortality has drawn attention to the potential role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) because the SARS-CoV-2 uses the ACE2 receptor as its point of entry into the body. It is not clear if and to what degree the SARS-CoV-2 virus affects the renin-angiotensin system. Early studies from China which speculated on the role of ACE inhibition and ARBs did not evaluate the drug regimens. A vast body of evidence supports the use of ACE inhibitors and ARBs in hypertensive patients and patients with heart failure, and very little evidence has been acquired about their role in COVID-19. There is good evidence in support of the use of ACE inhibitors and ARBs in indicated patients with hypertension and heart failure, and clinicians should be reticent about abruptly withdrawing these drugs based on a paucity of evidence.

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Early observations from the ongoing pandemic reveal that patients with cardiovascular risk factors are at elevated risk of adverse outcomes. Based on theoretical models of the renin-angiotensin system (RAS), and its suspected interaction with the novel coronavirus, suspicions have arisen about the use of certain pharmacologic agents during the coronavirus 2019 (COVID-19). This paper explains what is known about the pathophysiological mechanisms and provides a statement with respect to their clinical management.

The angiotensin-converting enzyme 2 (ACE2) has been identified as the receptor for the severe acute respiratory syndrome (SARS) coronavirus, and it appears likely that it is also the receptor for the novel SARS-CoV-2 virus associated with the COVID-19 pandemic.^{1,2} The ACE2 receptors bind to the spikes on the coronavirus and support syncytia as the virus injects its RNA to hijack the cell. A murine study found that ACE2-knockout mice are SARS resistant.³ Indeed, the ACE2

receptor appears crucial to SARS infection *in vivo*.⁴ It is presumed that the ACE2 receptor functions in similar fashion with the COVID-19 virus, but this remains unproven.

In addition to high expression in the epithelial cells of the lungs, intestines, kidneys, and blood vessels,² a recent study also found a high expression of ACE2 receptors in the epithelial cells of the mucosal cells of the oral cavity.⁵ An intriguing commentary by Fang et al.,⁶ suggested that based on early data from Chinese patients, those with hypertension, diabetes, or both might be at elevated risk for COVID-19 infection. However, none of the earlier studies and reports published by the Chinese colleagues evaluated the pharmacologic regimens of the patients. The hasty response against specific drugs in the setting of COVID-19 has been effectively challenged as being speculative rather than evidence based.⁷

Results from several Chinese reports are summarized in Table 1. None of these studies described drug regimens of these patients. A study from Korea (n = 28) found that 36% of the confirmed COVID-19 patients in the study had at least one underlying disease including hypertension, diabetes, asthma, chronic rhinitis, dyslipidemia, or hypothyroidism; one patient in this study had been treated for lung cancer.⁸ A meta-analysis of COVID-19 in China (n = 1527 patients, 6 studies) reported that of the hospitalized patients, 17.1% had

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Key Points**Background:**

- Early studies from China implicated angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers as being potentially of risk in coronavirus 2019 patients, but this evidence is not based on actual drug use patterns.

Findings:

- ACE inhibitors and angiotensin-receptor blockers are important drugs for the treatment of hypertension and heart failure, and a vast amount of evidence supports their use; they should not be abruptly withdrawn based on a paucity of evidence.
- The SARS-CoV-2 virus enters the body through the ACE2 receptor.

hypertension, 16.4% had cardiac or cerebrovascular disease, and 9.7% had diabetes, but the rates were 2- to 3-fold greater among COVID-19 patients in the intensive care.⁹

None of these studies specifically evaluated the use of ACE inhibitors or other medications in COVID-19 patients, but the speculation is that patients with such comorbidities would often be treated with ACE inhibitors. Fang et al.,⁶ then proposed that ACE inhibition upregulates ACE2, which, in turn, would facilitate COVID-19 infection. This has focused attention on the role of the RAS in the context of coronavirus.

RAS, which maintains blood pressure homeostasis, is an enzymatic cascade that uses renin produced by the kidneys to transform angiotensinogen (Ang) into AngI. AngI is catalyzed by ACE enzyme to produce AngII, which is catalyzed by the ACE2 into Ang1-7 and Ang1-9.^{15,16} While AngI is physiologically inactive, AngII, catalyzed by the ACE enzyme, is a vasoconstrictor and regulates aldosterone secretion.¹⁶ Pharmacologic inhibition of the ACE enzyme using drugs such as captopril, enalapril, lisinopril, or other ACE inhibitors, are frequently used to treat hypertension and heart failure.¹⁶ It should be noted that in the conversion of AngI into AngII, the ACE enzyme inactivates the vasodilating peptides bradykinin and kallidin.¹⁷

The ACE2 enzyme was first discovered in 2000 and remains to be more fully elucidated. There are distinct

differences between ACE and ACE2, the 2 key enzymes of the RAS. ACE is a dipeptidyl carboxypeptidase while ACE2 is a carboxypeptidase. ACE2 appears to be a chimeric protein.¹⁸ ACE2 cleaves only a single C-terminal residue from the peptide substrate and cannot cleave to bradykinin or other ACE substrates; ACE2 does not appear to be susceptible to pharmacologic ACE inhibition.¹⁹ Because ACE2 is a type I transmembrane protein with a large catalytic extracellular domain, it can act as a peptidase or viral receptor. Its extracellular domain can be cleaved from the cell surface by other peptidases and the enzymatic activity on the cell surface may be modulated by S-protein binding and clustering in "lipid rafts" or microdomains.²⁰ A murine study found that pharmacologic ACE inhibition upregulated ACE2 in rats with hepatic fibrosis, both *in vivo* and *in vitro*.²¹

ACE enzymes are abundant and widely distributed in the body. At first, it was believed that ACE2 enzymes were found only or mainly in the heart, kidney, and testes,²² but it appears they are also found in the intestines, epithelia of the lungs, and oral mucosa.^{5,23,24} In fact ACE2 may be far more abundant in the body than originally thought. The ACE2 enzyme is thought to play a role in cardiac function, the endocrine system, and blood pressure.²⁵

As ACE2 was only recently discovered and much remains unknown about the angiotensin enzymatic cascade, it is not immediately clear how the novel SARS-CoV-2 virus might affect RAS, if indeed ACE2 is its viral receptor. Further questions arise, such as the potential role of ACE2 polymorphisms in the context of COVID-19 and other emerging coronaviruses. Are some people genetically predisposed to a more severe form of infection? If this is the case, it could possibly explain the patterns of COVID-19 outbreaks. Would other emerging coronaviruses also use ACE2 as the viral receptor? This makes it crucial to gain a better understanding of ACE2, RAS, and viral infections. Another key question is whether or not pharmacologic ACE inhibition, which increases ACE2 in the body, might either increase a person's risk of contracting COVID-19 or, alternately, exacerbate COVID-19 infection once it occurs. Such knowledge has life-saving ramifications in that hypertension, ischemic cardiac disease, and heart failure are prevalent conditions often treated with ACE inhibitors.

In these challenging days of trying to manage acute cases of COVID-19 infection, it is important to focus our future attention on greater understanding of the coronavirus infection and its interactions with RAS. Coronavirus infections, including SARS, Middle Eastern Respiratory Disease, H1N1, and others have emerged in the recent years, and there is no reason to

Table 1

Emerging studies on patients with severe COVID-19 and the rates of diabetes, hypertension, and cerebrovascular disease

Study	Diabetes (%)	Hypertension (%)	Cerebrovascular disease (%)
Yang et al. 2020 ¹⁰ 32 nonsurvivors from a cohort of 52 intensive-care patients	22	Not stated	22
Guan et al. 2020 ¹¹ 173 patients with severe disease from a study of 1099 patients	16.2	23.7	2.3
Zhang et al. 2020 ¹² 140 hospitalized patients	12	30	Not stated
Deng et al. 2020 ¹³ 26 fatal cases	42	54	15
Wu et al. 2020 ¹⁴ 201 patients who developed acute respiratory distress syndrome or died	19.0	27.4	Not stated

Abbreviation used: COVID-19, coronavirus 2019.

think that this is the final novel coronavirus to break the species barrier and infect humans. It is likely (but not known) that emerging coronaviruses will affect ACE2 and RAS, which is crucial to blood pressure homeostasis and respiratory health. Research is urgently needed and should be generously funded to avert potential future—and economically devastating—pandemics.

Clinical perspective

The social–media-driven amplification of concerns about ACE inhibitors and angiotensin-receptor blockers (ARBs) in the current pandemic are based on speculations about mechanisms that have not been elucidated. In fact, some patients have stopped taking their prescribed medications in the light of this news. For that reason, it is crucial that it be stated that while there is no evidence that supports the interaction between the RAS and the SARS-CoV-2 virus, there is abundant scientific evidence and clinical experience supporting the fact that ACE or ARB treatment is beneficial to people with cardiovascular risk factors. Indeed, preexisting heart failure is likely to worsen with COVID-19 and myocarditis with reduced ejection fraction has been reported, so it is of utmost important to continue the ACE or ARB regimen. Based on current knowledge, there is no reason to discontinue these important drugs, which are a cornerstone of modern cardiology. Please, colleagues, hold your horses! Patients who express concern about ACE inhibitors or ARBs should be reassured that these drugs are and remain important even during this pandemic, based on the best available scientific evidence. These drugs should not be withdrawn on this unscientific speculation. In this and many other matters, science and evidence will save lives.

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