

ACEI/ARB therapy during COVID-19 pandemic

Alexandra Paval*, Maria Dorobantu

Cardiology Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

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Abstract

The coronavirus disease 2019 (COVID-19) epidemic was caused by an infection with a new type of coronavirus, that is responsible for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and unfortunately, continues to endanger global health. Although the clinical manifestations of COVID-19 predominate in the respiratory system, some patients may also have severe cardiovascular (CV) damage. Research conducted over the past several months have indicated that patients with cardiovascular diseases are at a higher risk of complications and mortality from SARS-CoV-2 (1). Recently, the main concern for all has been to identify a causal relationship between the use of RAAS (renin-angiotensin-aldosterone system) inhibitors (angiotensin converting enzyme inhibitors -ACEIs, and angiotensin II receptor blockers- ARBs) in patients infected with COVID-19 and the course of this infection. It had also been speculated that these agents could increase the susceptibility to contracting COVID-19. Although much research has been done over the past two months, the use of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) remains an open topic of major interest to clinicians treating COVID-19 in patients with cardiovascular disease. After a detailed analysis of the data, recent studies have revealed a theoretical benefit of ACEIs / ARBs in patients infected with SARS-CoV-2, but we opine that there is not yet strong enough evidence to support a correlation. What is well known so far is that the withdrawal of these drugs from the scheme of patients with chronic cardiovascular disease could be detrimental to the evolution and complications of this COVID-19 infection.

Keywords: ACEI, ARB, ACE2 receptor, COVID-19, hypertension, SARS-CoV-2.

Abbreviations: ACEIs (angiotensin-converting enzyme inhibitors), ACE (angiotensin-converting enzyme), ARBs (angiotensin receptor blockers), ARDS (acute respiratory distress syndrome), CV (cardiovascular), RAAS (renin-angiotensin-aldosterone system), TMPRSS2 (Transmembrane Serine Protease 2), SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2).

Introduction

There have been approximately 4,5 million cases reported and more than 300000 deaths due to COVID-19 across 216 countries worldwide at the time of this writing. (2)

*Correspondence to: Paval, Alexandra,
Carol Davila University of Medicine and Pharmacy,
8 Eroii Sanitari Blvd, Bucharest, 050474, Romania

Recently, studies have shown that SARS-CoV-2 has major implications for the CV system. Patients with multiple CV risk factors, including hypertension, as well as patients with established CV disease (preexisting coronary artery disease, arrhythmias, a history of heart failure, as well as chronic lung disease such as chronic obstructive pulmonary disease, have been identified as particularly vulnerable populations, with increased morbidity and mortality, if infected with COVID-19. (3) First review of patients characteristics from China among SARS-CoV-2 infected patients, revealed that hypertension, cardiovascular diseases, and diabetes mellitus are highly prevalent, and may be associated with unfavorable clinical course. (4) It is known that patients with these diseases are often treated with RAAS inhibitors, respectively ACEIs or ARBs, proving their efficacy in multiple studies.

Considering the reports from the countries with a large number of cases (data reported from Italy), where the prevalence of hypertension among those infected with COVID-19 was 73% (5), as well as the fact that most hypertensive patients worldwide are treated mainly with ACEIs or ARBs, the research has focused more on this pathology. Hypertension is a major risk factor of global mortality, and its importance has recently been investigated in the context of the novel SARS-CoV-2, as well as the consequences of treatment with ACEIs/ARBs in patients infected with CV disease. Hypertension was usually observed as a frequent comorbidity in adult patients, particularly in the elderly, age over 65 years, hospitalized for COVID-19. In a study published by Juyi Li et al, they found that patients with hypertension had more than 3 times the mortality rate of all other patients hospitalized with COVID-19 (6). Available studies do not provide sound evidence that hypertension is an independent risk factor for lower respiratory tract infections. However, the researchers point out that high blood pressure contributes to the increased incidence of cardiovascular events in these patients. (7). What is proved is that the use of ACEIs and ARBs might be associated with a lower incidence of community-acquired pneumonia and improved outcome in patients with lower respiratory tract infections. This also has been demonstrated in viral pneumonia, in which RAAS blockers have been associated with improved pneumonia-related outcomes. (8)

Recent discussions and research have sought to understand the effects of ACEI and ARB in patients infected with COVID and the mechanisms that may influence the course of the disease in patients taking these drugs.

The infectious agent that causes Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), Covid-19, has been shown to enter the host cell through a cellular receptor - angiotensin 2 con-

verting enzyme (ACE2). (9) Entry of the virus into these cells is facilitated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE2 receptor. (10) The enzyme ACE2, a new homologue of the enzyme ACE, is a membrane-bound monocarboxypeptidase with high expression in the heart and lung tissue, but also expressed in the kidney, intestine and endothelium (11,12), which can convert Ang II to Ang(1-7), with a vasodilating effect, or convert Ang I to Ang(1-9). (13,14,15). ACE2 receptor appears to counter-regulate RAAS activation by degrading Ang II (16), but is not inhibited by ACE inhibitors (17). Data from animal clinical trials cannot be extrapolated to humans because in animals, the expression of receptors inside the cell is predominantly compared to the human model, where the circulating or soluble ACE2 receptor is analyzed.

At the beginning of the pandemic, two opposite hypotheses have been proposed for the results of RAAS inhibition with ACEIs or ARBs (18), considering ACE2 levels as a double-edged sword. On the one hand, in the harmful hypothesis, RAAS inhibition increases ACE2 expression at the cell surface, thus promoting SARS-CoV-2 entry (13), may facilitate infection and increase the risk of developing severe and fatal COVID-19. (19) On the other hand, in the hypothesis of the beneficial effect, inhibition of RAAS reduces the production of Angiotensin II (which, otherwise, upon SARS-CoV-2 binding, would activate AT1R), thus decreasing inflammation and pulmonary fibrosis, with a protective effect on acute lung damage. Based on these hypotheses, the researchers carefully analyzed the impact of renin-angiotensin-aldosterone inhibitors in patients infected with SARS-CoV-2. RAAS inhibitor therapy has a different impact on the components of this hormonal system, either acting directly or through feedback loops. Although ACE2 is not a direct target of ACEIs, because it does not bind and inhibit the active site of ACE2, an increase in ACE2 expression has been demonstrated during ACEI or ARB therapy. (20)

The renin-angiotensin-aldosterone system (RAAS) is a hormone system and plays a essential role in maintaining normal cardiovascular functions through its effects in regulating blood pressure and electrolyte balance (21) and it widely implicated in hypertension, coronary heart disease, myocarditis, and heart failure. (22) Basically, RAAS consists of angiotensinogen, renin, angiotensin II (Ang II) acting on Ang II type 1 receptors (AT1Rs) and type 2 receptors (AT2Rs) and angiotensin converting enzyme (ACE). (23,24). ACE is present mainly in type 1 and type 2 pneumocytes, but also in endothelial cells, kidney epithelial cells, and the brain and is an enzyme that plays a role in the generation of Ang II by catalysing conversion of the Ang I.

The principal mechanism of ACE- Inhibitors is the blocking of the angiotensin converting enzyme (hence the “ACE-Inhibitors” name), which in turn converts Angiotensin I into in an octapeptide called Angiotensin II. Following the known path of the RAAS by blocking the formation of angiotensin II, ACEIs also block the secretion of aldosterone. The main actions of aldosterone are the salt and water reabsorption as well as the excretion of potas-

sium (that is why for example, a common side effect of ACEIs is hyperpotassemia). By regulating the Aldosterone-level, ACEIs have consequently effects on water retention, blood pressure and blood volume. Furthermore, decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodeling of smooth muscle and cardiac myocytes (25). In the context of COVID-19 pandemic, the ACE-Inhibitors have raised great inter-

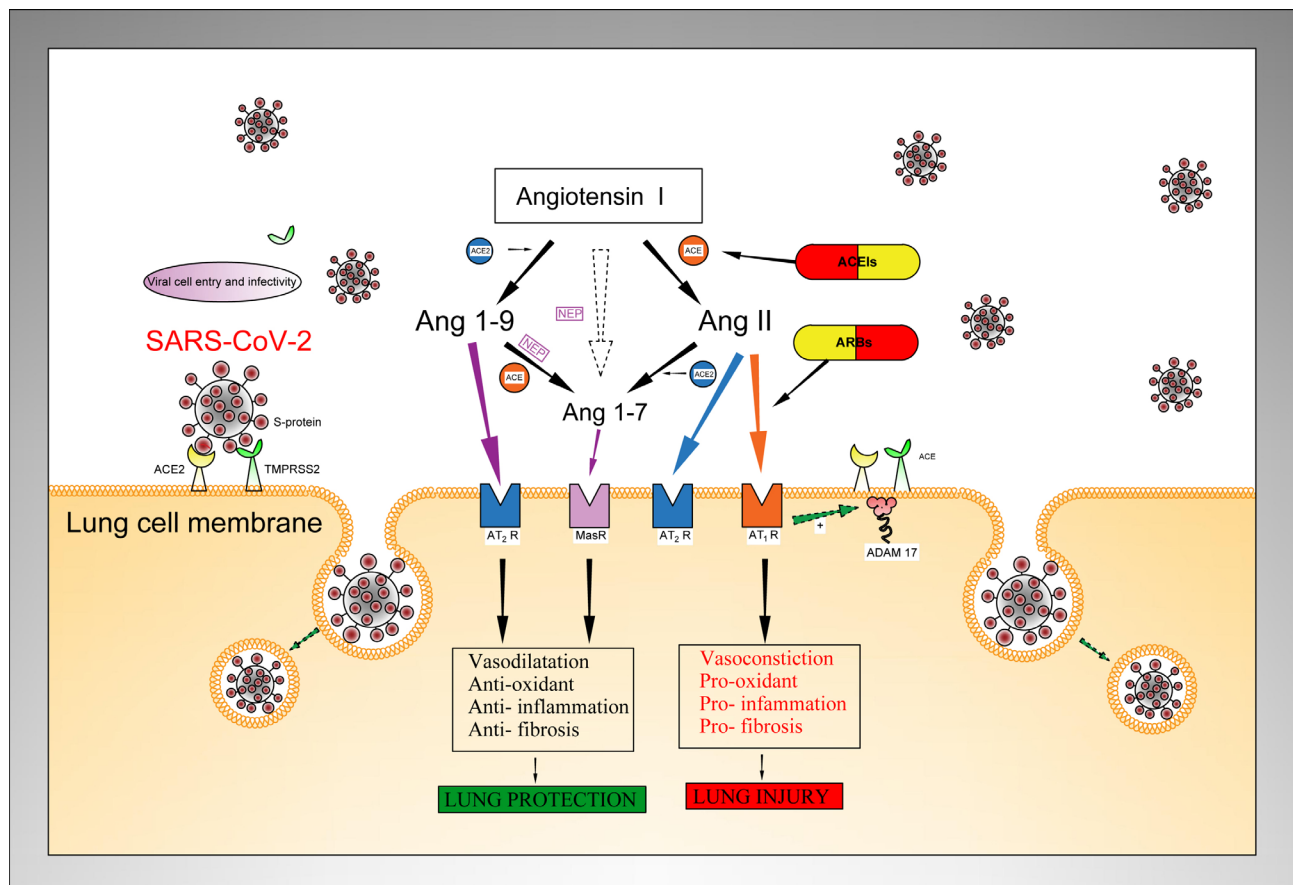


Figure 1. Schematic representation of the role of ACE2 as the main element in the counter-regulation of the renin-angiotensin system in the lung. The ACE2 receptor is expressed on the alveolar epithelial cells, and serves as co-transporter for virus to enter in the target cells. The spike protein of SARS-CoV facilitates viral entry into host cells, binds to ACE2 in the cell membrane and thus promote the penetration of viral cells into cells and their subsequent replication. The enzyme ACE2 is cleaved by ADAM17, becoming a soluble form released in body fluids, with opposite lung effects compared to the Ang II - AT1R complex, by activating MasR and AT2R receptors. (31) ACE2 induces vasodilation by increasing Ang 1-7 synthesis and by reducing Ang II effects. Ang 1-7, can also be generated by neutral endopeptidase (NEP), also with protective effects. Ang 1-7 binds to MasR, thus releasing nitric oxide, activating baroreflex sensitivity and producing other protective effects on tissues in the cardiovascular system. Any action of decreasing the activity of ACE2 in the lungs leads to the activation of the Ang II - AT1R axis, with harmful effects. Moreover, SARS-CoV-2 requires a cellular serine protease TMPRSS2, which will transform SARS-CoV-2 by enzymatic cleavage of the spike protein and support cell entry. Therapy with ARBs or ACEIs modulate several components of the RAS either directly or by affecting feedback loops. Treatment with ARBs protects against lung injury by AT1R receptor blockade. ACEIs, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; ARNI, angiotensin receptor neprilysin inhibitor; AT1R, angiotensin II receptor type 1. AT2R, angiotensin II receptor type 2; MasR, Mas receptor; RAAS, renin–angiotensin-aldosterone system; Adapted from Reinhold Kreutz (Hypertension, the renin–angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19).

est, since previous studies have shown that ACE2 represents the key receptor for SARS-CoV entry into target cells by binding with its spike protein to ACE2. (26) Add-on, SARS-CoV uses the cellular serine protease TMPRSS2 as a cofactor for cell entry by priming of the spike protein. (9) SARS-CoV-2 depends on co-expression of these two proteins, both ACE2 and TMPRSS2, which are needed to acquire infectivity. (27) From the data so far, ACEI treatment can protect the lung by reducing the level of Ang II by inhibiting the conversion of Ang I to Ang II.

The mechanism of cardiac damage in patients with COVID-19 is unclear but this interaction of SARS-CoV2 with ACE2 may have a role and can result in changes of ACE2 pathways leading to acute injury to the lung, heart, and endothelial cells (28). To better highlight the role of ACE2, numerous studies have been conducted, and the resulting evidence supports its protective role in cardiovascular disease. In a study of atherosclerosis-prone apolipoprotein E knockout mice, ACE2 deficiency was shown to result in an increased inflammatory response, leading to increased atheroma plaques. (29) Also, Sarkissian et al., in animal studies, identified that cardiac overexpression of ACE2 led to a protective influence on the heart during myocardial infarction by preserving contractility and cardiac function. (30)

Besides systemic function, angiotensin-converting enzyme 2 (ACE2) also considered as the host cellular receptor of SARS-CoV-2, has been identified in multiple organs, but its cellular distribution in human heart is not explained clearly. One study performed the first state-of-art single cell atlas of adult human heart, and detect that pericytes with high expression of ACE2 might act as the target cardiac cell of SARS-CoV-2 (32) It is suggested that the risk of coronavirus infection is high, at least due to high ACE2 expression in populations with a high CV risk.

In animal model studies with severe lung damage, an association between Ang II-AT1R axis activation and the severity of these lesions has been demonstrated, with down-regulation of ACE2, while increased ACE2 / Ang 1-7 expression counterbalances these harmful effects. (33) Another characteristic pathogenic link demonstrated in acute respiratory distress syndrome (ARDS) in mice was increased vascular permeability, particularly pronounced in ACE2-deficient mice. (34) Decreased ACE2 expression and potentiation of Ang II - AT1R axis activation leads to aggravation of lung lesions. (33)

Ang II induces internalization of ACE2, and thus reduces tissue expression. Over time, from animal studies, it has been shown that some ARB (losartan) prevent this through interaction and sta-

bilization of ACE2 with AT1 receptors (9) and that means that ARBs could reduce SARS-CoV-2 cell entry by reducing availability of binding sites. To date, there is no clear evidence of ACE2 up-regulation associated with these drugs in humans. (32)

Angiotensin II receptor blockers (ARBs), another first-line therapy for high blood pressure, could inhibit Ang II actions by selectively binding AT1 receptors in vascular smooth muscle, resulting in lowering blood pressure and preventing major cardiovascular events. (35,36) Studies to date in both humans and rats have suggested that ARBs may regulate ACE2 levels (37,38). Recent discussions in the midst of the coronavirus pandemic highlight that ARB and ACEI could be used as therapy to reduce the aggression and mortality caused by COVID-19 infection. (39)

Given the myocardial damage that can occur in COVID-19, stopping these drugs unless there is another clinical reason to suspend them, significantly increases the rate of morbidity and mortality for these patients.

Recently, many studies have reported data showing that there was no difference in the disease progression and the risk of death for COVID-19 if using of ACEI / ARB among those with severe and non-severe disease. Furthermore, there was no difference in comorbidities associated with hypertension and length of hospital stay in patients taking ACEI / ARB or non-ACEI / ARB.

Although it is possible that an increase in ACE2 by inhibiting RAS increases the theoretical risk of being more susceptible to the disease, there are currently no data to establish a causal relationship between ACE2 activity and SARS-CoV-2-associated mortality. Moreover, there are data to support the fact that ACE2 expression cannot necessarily be correlated with the degree of infection. Although the presence of ACE2 is currently considered mandatory for SARS-CoV-2 infection, recent analyzes have shown that in some cell types expressing ACE2, SARS-CoV-2 was absent, as well as the fact that cells that were apparently without ACE2, infection was present. This actually suggests that some co-factors may be needed to promote the infection. (40)

Although the data available so far are incomplete, a general effect on lung tissue protection could be further promoted by ACE2 modulation.

Conclusions

Despite the fact that these theoretical hypotheses regarding pharmacologic regulation of ACE2 could have an impact on SARS-CoV-2 infectivity, there is a clear inherent risk for impairment related to the removal of RAAS inhibitors in stable patients. Over

time, several studies have shown that RAAS inhibitors play an important role in protecting the myocardium and kidneys, and their discontinuation can cause clinical decompensation in high-risk patients. In addition, RAAS inhibitors are a cornerstone in the treatment of myocardial infarction, reducing early mortality. (41)

Based on the evidence available at this time, taking into consideration the theoretical concerns and the degree of uncertainty regarding the possible effect of RAAS inhibitors on ACE2, as well as the way in which these drugs could potentiate the severity of the disease, the majority of the authors pleads for the continuation of using RAAS inhibitors for those patients in otherwise stable condition who are exposed to risk, evaluated for, or have Covid-19. (42)

Given the contradictory hypotheses and rapidly evolving nature of this disease, several cardiology associations (ESC Hypertension Council and ACC / AHA) issued an official statement regarding the therapy with ACEI or ARB for COVID-19 patients.

Cardiovascular disease, especially hypertension combined with diabetes and/or chronic kidney disease, would predispose patients to an increased risk of COVID-19 severity and mortality. Therefore, patients with these underlying conditions who develop COVID-19 should be monitored very carefully and any recommendation should only be made particularly, after there is a clear clinical judgment and should be adjusted as needed to correspond with the latest scientific evidence. It is very important for cardiac patients to follow the previously prescribed treatment with these drugs for chronic disease management, so as not to suffer decompensation, much more difficult to manage during this period.

All these data support current guidelines and societal recommendations for treating cardiovascular disease during the COVID-19 pandemic.

Undoubtedly, further research is required to clarify the controversies regarding the position of ACEI/ARB in pandemic COVID-19.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

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