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Role of age, comorbidity and renin-angiotensin-aldosterone system in COVID-19. Effects of ACE inhibitors and angiotensin receptor blockers

The review addressed the relationship of coronavirus disease 2019 (COVID-19) with functioning of the renin-angiotensin-aldosterone axis and the causes for unfavorable prognosis depending on patients' age and comorbidities. The authors discussed in detail potential effects of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists on the risk of infection and the course of COVID-2019 as well as the effect of SARS-COV2 virus on the cardiovascular system.

Keywords COVID-19, ageing, ACE inhibitors, angiotensin II receptor antagonists, cardiovascular system

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This pandemic of coronavirus disease 2019 (COVID-19) caused by a new coronavirus known as SARS-CoV-2 has raised a number of issues about the functioning of the renin-angiotensin-aldosterone system (RAAS) and its role in the development and progression of the disease. Angiotensin-converting enzyme (ACE) stimulates the synthesis of angiotensin II with its high vasoconstrictor, proliferative, and pro-inflammatory power increasing with age [1]. Type 2 ACE (ACE2) is responsible for transforming angiotensin II into angiotensin 1-7 that has anti-inflammatory properties and stimulates the synthesis of nitric oxide, which in turn has vasodilating and vasoprotective properties (Figure 1) [2].

SARS-CoV-2 enters the cell and attaches to ACE2, mostly located on cell membranes, including the pulmonary epithelium (Figure 1). To penetrate the cell, the virus needs not only ACE2 but also a transmembrane protease, serine 2 (TMPRSS2) (Figure 1) [3]. Moreover, ACE2 is not always located on the cell membranes, so the virus is able also to attach to free ACE2.

Age and underlying cardiovascular diseases in COVID-19

During the pandemic, a popular hypothesis is that COVID-19 affects most often elderly people and those who have a concomitant pathology, e.g., hypertension, and/or diabetes mellitus (DM). However, there is no actual evidence for this. The activity of the main components of RAAS, including angiotensin II, increases significantly with age and predominantly in the presence of hypertension and DM [4–6], and an imbalance occurs between pro-inflammatory angiotensin II and anti-inflammatory angiotensin 1–7 [7, 8]. Such an imbalance is a factor determining polyorgan pathology, systemic inflammation, organ remodeling, and a much more severe course of the disease. Based on the fact that the expression of ACE2 was shown in animal models to decrease with age [9], Al Ghatrif et al. suggested that the risk of severe acute respiratory syndrome (SARS)-CoV-2 infection may even decrease in elderly patients compared to young patients [7]. However, it should be noted that no age-dependent differences were found in the ACE2:ACE ratio in bronchoalveolar lavage fluid collected from mechanically ventilated patients with non-COVID-19 acute respiratory distress syndrome, which contradicts the experimental data [10].

Patients over 65 years of age had significantly increased levels of pro-inflammatory cytokines, including myeloperoxidase, interleukin-6, interleukin-10, and P-selectin, which indicates greater severity of neutrophilic infiltration and inflammation [10]. The latter may be one of the reasons for the severe course of the disease in elderly patients. Also, a small-sample, Chinese study showed that patients with COVID-19 had increased angiotensin II, and the degree of increase was associated with the severity of lung injury and viral load [11].

In younger patients, angiotensin II and angiotensin 1–7 activity [8], as well as, apparently, ACE and ACE2 activity, appears to stay at normal levels. The balance is preserved between vasoconstrictor and inflammatory factors stimulated by angiotensin II on one hand and the formation of nitric oxide and blockade interleukin-6 maintained by angiotensin 1–7 on the other hand. This is one of the factors of a milder course of the disease. However, the gate for the virus is not closed, which means the incidence and infectiousness are high in young patients.

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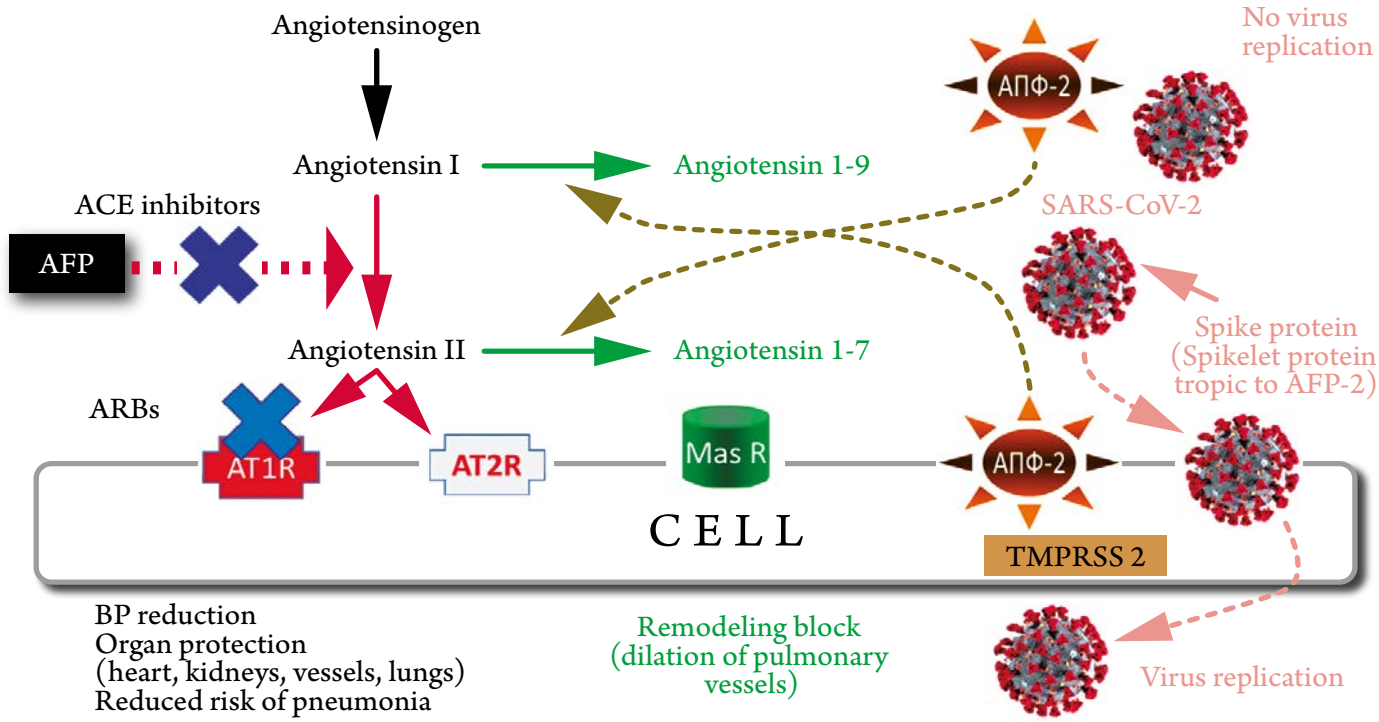
Figure 1. The RAAS system and the mechanism of cell penetration by SARS-CoV-2



This is confirmed by the 2003 epidemic of SARS [12], caused by a similar SARS-CoV-1 virus, and also by comparisons of morbidity and mortality from COVID-19 in South Korea and Italy during March 2020 [13]. In Italy, where SARS-CoV-2 was tested mainly in the severe course of the disease, it is not surprising that the mortality exceeded 10%, since almost 60% of patients were over 60 years old, and 19% were over 80 years old. In the Lombardian cohort of patients, one additional disease was reported in 68%, and the incidence of hypertension was 49% [14]. The incidence of hypertension was higher in the deceased group (63%, 195 of 309 patients) versus the group of patients discharged from the intensive care unit (40%, 84 of 212 patients). The difference of 23% was highly significant [95% confidence interval (CI): 15–32%] ($p<0.001$). Mortality was also higher in patients over 63 years old (36%) versus patients ≤63 years old (15%) ($p<0.001$).

In South Korea, where testing was as extensive as possible and included all who contacted confirmed patients with different courses of the disease, 74% of patients were younger than 60 years old, and mortality was about 1%. According to demographic data, 22% of the South Korean population is ≥ 60 years old, and 26% of patients with COVID-19 were in this age group. Interestingly, according to the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), as of April 4, 80% of Russian patients with COVID-19 were less than 60 years old. Also, according to the Moscow COVID-19 Combating Headquarters, as of April 6, 84% of new cases of COVID-19 were registered in people less than 65 years old [15]. At the same time, 15.6% of the Russian population is over 65 years old.

If we look at the Chinese data, on February 11, 2020, it was reported that 68.8% of patients with confirmed COVID-19 diagnosis were younger than 60 years old [16]. The total mortality rate was 2.3%, with 8.0% in patients 70-79 years old and 14.8% in patients ≥80 years old. The mortality rate also increased in patients with cardiovascular diseases (10.5%), DM (7.3%), hypertension (6%), and chronic pulmonary diseases (6.3%) [17]. In the Wuhan cohort, 49% of patients with COVID-19 had at least one concomitant disease, most commonly hypertension (30%), DM (19%), or coronary artery disease (CAD) (8%). Multi-factor analysis showed that the predictors of death were age (odds ratio (OR) 1.1 per year), high Sequential Organ Failure Assessment (SOFA) scores (OR=5.65), and elevated D-dimer more than 1 μg/ml (OR=18.42) [18]. Interestingly, only univariate analysis showed a reliable increase in the risk of death in the presence of cardiovascular comorbidity (21.4-fold for CAD, 3.05-fold for hypertension, and 2.85-fold for DM).

Thus, we can suggest that the incidence rate in young patients. i.e., less than 60–65 years old, is comparable to that in elderly patients. However, in most cases, the course of the disease in younger patients is relatively mild, due, at least in part, to the preserved protective function of the ACE2 system and the balance between angiotensin II and angiotensin 1–7. The course of the disease in patients more than 60 years old and with concomitant hypertension and type 2 DM is much more severe due to systemic inflammation supported by the predominant activity of ACE and the production of more angiotensin II. Therefore, it seems reasonable to study the possibility of using drugs that affect RAAS, specifically ACE inhibitors and

angiotensin II receptor antagonists (ARBs) to treat patients with COVID-19 and concomitant pathologies.

COVID-19 and the use of ACE inhibitors and ARBs

Considering that SARS-CoV-2 enters cells mainly via ACE2 receptors, some debate has arisen as to whether ACE inhibitors and ARBs have a potential effect on the risk of infection and on the course of the disease. At the same time, there are opinions both about the potential harm [19] and the benefits of using these drugs [20, 21].

Strictly speaking, ACE inhibitors have an effect on ACE1, which converts angiotensin I into angiotensin II; ARBs block angiotensin II type 1 receptors (Figure 1). Thus, they have organoprotective, vasodilatory, and anti-inflammatory effects. Considering that the expression of ACE is maximal in the lungs, these effects of contemporary RAAS inhibitors can contribute to the decrease in the pulmonary lesion [22]. However, ACE inhibitors and ARBs do not have a direct impact on the activity of ACE2, which converts type I and type II angiotensin into angiotensin 1-7 with its protective anti-inflammatory properties. Some animal studies have shown that ARBs and ACE inhibitors increased the expression of ACE2 [23–25], although this was not confirmed in other studies [26, 27]. Analysis of clinical studies also does not provide immediate clarity on whether the levels of ACE2 increase in patients treated with ACE inhibitors and ARBs [28].

We should keep in mind that a reactive increase in the ACE2 levels during the use of ACE inhibitors and ARBs, even if it occurs, does not imply automatically that it will cause a higher risk of infection. The following factors are relevant: 1) Every person has ACE2. Moreover, it is expressed in epithelial cells of the oral and tongue mucosa [29], which make it much easier for the virus to penetrate these tissues. 2) The virus needs not only ACE2 but also a transmembrane protease, serine 3 (TMPRSS3), to penetrate the cell [3] (Figure 1). The possibility of using a TMPRSS3 inhibitor to treat patients with COVID-19 is under discussion. 3) ACE2 is not entirely bound to cell membranes (Figure 1). At the same time, if the virus attaches to ACE2, which is not bound to the cell membrane, this may reduce the transmission rate [30]. A study using recombinant ACE2 to treat COVID-19 has been scheduled [31]. We wish to point out that the use of recombinant ACE2 can slow down the development of infection by activating the potentially protective effects of ACE-2 [32] associated with increased nitric oxide and decreased pro-inflammatory cytokines. Thus, there is no reason to argue that increased ACE2 will necessarily increase the risk of infection.

A natural question arises as to whether ACE inhibitors and ARBs have protective effects in COVID-19. There are currently few published findings of studies or analyzes of patients with a view as to whether they received concomitant treatment with RAAS inhibitors. Four available papers are listed in Table 1. It is worth noting that three of the four papers published on https://www.medrxiv.org/ are preprints. This site publishes articles before review to quickly exchange information during the pandemic.

Table 1 shows that in two of the four papers [33, 34], the use of ACE inhibitors/ARBs was accompanied by a reduced risk of death and transfer to an intensive care unit. Multivariate analysis found this effect statistically significant. The other two studies [35, 36], which were smaller than the first two, detected no statistically significant difference in event risk among patients who took or did not take ACE inhibitors/ARBs. One of these papers noted a statistically significant reduction in the risk of severe lung injury in COVID-19 in patients over 65 years old taking ARBs. Interestingly, Yang et al. also reported lower levels of C-reactive protein and procalcitonin [36], and Zhang et al. reported a smaller incidence of septic shock, based on multivariate analysis, odds ratio 0.36, 95% CI [0.16–0.84] (p=0.01).

It should be borne in mind that all papers described are observational studies, and despite adjustments for the differences in characteristics between patients who took or did not take ACE inhibitors/ARBs, the lower risk of death when using ACE inhibitors/ARBs may be related to the presence of unrecorded differences rather than the effect of the drug.

What is the protective mechanism of ACE inhibitors and ARBs in patients with COVID-19? In coronavirus-induced lung diseases, ACE2 levels may decline, and angiotensin II levels significantly elevate [2, 11], which is seen as one of the key mechanisms resulting in damage to the lung and possibly other organs, including the heart. Animal experiments showed that the use of losartan reduces the risk of lung damage caused by a similar coronavirus (SARS-CoV-1) [2]. An Randomized clinical trial is scheduled to study the possibility of using losartan to reduce the risk of complications in patients hospitalized for COVID-19 [37]. This study also plans to assess 28- and 90-day mortality. Another losartan study is planned in patients with COVID-19 who do not require hospitalization to prevent the progression of viral infection or to reduce the risk of involving the heart and lungs in the pathological process [38].

It should also be noted that a meta-analysis of both RCIs and observational studies showed a decrease in the risk of pneumonia during the administration of ACE inhibitors. However, this analysis did not distinguish between viral and bacterial pneumonia, and the detected effect in non-randomized studies could have been related to different characteristics of patients who received or did not receive ACE inhibitors [39].

Moreover, COVID-19 can also cause heart damage, and in this case, the patients' prognosis may deteriorate. A series of observations of patients with COVID-19 carried out in China showed that the risk of acute myocardial injury and ventricular heart rhythm disorders was 7.2 and 16.7%, respectively [40]. Experimental data showed an increase in the expression of ACE2

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Table 1. Observational studies comparing the outcomes of patients with COVID-19 who used or did not use ACE inhibitors/ARBs

Study	Design and study groups	Results
Yang et al. [36] 2020. 126 patients with hypertension admitted to the hospital. Collection of data: 05.01.20–22.02.20. The duration of observation was from the day of inclusion to 03.03.20. One hospital. China. Hubei.	A retrospective cohort study. The treatment group included 43 patients receiving ACE inhibitors/ARBs. The control group included 83 patients who did not receive ACE inhibitors/ARBs.	All-cause mortality in the ACE inhibitors/ARBs group was 4.7%, in the control group 13.3%, p=0.216. Patients in critical condition in the ACE inhibitors/ARBs group, 9.3%, in the control group, 22.9%, p=0.061.
Liu et al. [35]. 78 patients with hypertension admitted to the hospital. Collection of data: 27.12.19–29.02.20. Three hospitals. Hubei, Beijing, and Shenzhen. China.	A retrospective cohort study. The ARBs group included 22 patients who took ACE inhibitors/ARBs before infection with COVID-19. The control group included 56 patients on other blood pressure control drugs or no antihypertensive drugs before infection with COVID-19.	There was no difference in the disease severity in patients with hypertension who did not take antihypertensive drugs or took one of the following classes of drugs: ACE inhibitors, ARBs, beta-blockers, calcium antagonists, and thiazide diuretics. In the group of 46 patients over 65 years old, the use of ARBs before admission to the hospital reduced the risk of severe COVID-19. Univariate analysis odds ratio=0.343, 95% CI: 0.128 – 0.916; p=0.025. Multivariate analysis odds ratio 0.25, 95% CI: 0.064 – 0.976, p=0.046.
Bean et al. [34]. 205 patients admitted to the hospital. Collection of data: 01.03.20 – 22.03.20. The duration of observation was 7 days since the onset of symptoms. One medical center. GB. London.	A retrospective cohort study. The ACE inhibitors group included 37 patients who took ACE inhibitors for 7 days before the onset of symptoms and/or during hospitalization. The control group included 168 patients who did not take ACE inhibitors during this period.	14% (5/37) in the ACE inhibitors group and 29% (48/168) in the control group died or were transferred to the ICU. According to the univariate analysis, the odds ratio of death or transfer to the ICU in the ACE inhibitors group was 0.42, 95% CI: 0.14 – 1.00, p=0.058. According to multivariate analysis (age, sex, presence of hypertension, diabetes mellitus, CAD, CHF, DM), the odds ratio of death or transfer to the ICU in the ACE inhibitors group was 0.29, 95% CI: 0.10 – 0.75, p<0.01.
Zhang et al. [33]. 1128 patients with hypertension admitted to the hospital. Collection of data: 31.12.19 – 20.02.20. The duration of observation was 28 days from the day of hospitalization. Nine hospitals. China. Hubei.	A retrospective cohort study. The ACE inhibitors/ARBs group included 188 patients who took ACE inhibitors/ARBs during hospitalization. The control group included 940 patients who did not take ACE inhibitors/ARBs (745 of them took other antihypertensives).	The risk of death in the ACE inhibitors/ARBs group was 3.7%; in the control group, 9.8%, p=0.01. According to multivariate analysis (age, sex, comorbidities, therapy during hospitalization), the OR of all-cause death in the ACE inhibitors/ARBs group was 0.42, 95% CI: 0.19 – 0.92; p=0.03. Propensity match analysis showed that the OR of all-cause death in the ACE inhibitors/ARBs group was 0.37; 95% CI: 0.15 – 0.89, p=0.03.

ACE inhibitors/ARBs, the use of ACE inhibitors or ARBs; CI, confidence interval; OR, odds ratio; ICU, intensive care unit.

in the myocardium of patients with chronic heart failure [41], which may have contributed to cardiac lesions.

The main potential mechanisms of cardiac lesions in COVID-19 are [42]:

1) Increased local and systemic inflammation and hypercoagulation that increase the risk of plaque rupture, which can result in acute myocardial infarction.
2) Activation of the sympathetic system, causing increased oxygen consumption, which can contribute to myocardial ischemia.
3) Acute respiratory distress syndrome accompanied by development of severe hypoxia, reduced oxygen delivery to the myocardium, and heart rhythm disorders.
4) Direct injury of cardiomyocytes and the effect of inflammatory cytokines, which contribute to development of myocarditis and chronic heart failure [43].
5) Venous thrombosis and risk of pulmonary embolism.

Thus, there is no reason to cancel the main cardiovascular drugs in patients with COVID-19 and concomitant heart diseases if there are indications for their administration. This includes statins, beta-blockers, anticoagulants, and ACE inhibitors/ARBs [44]. While data about the treatment of such patients is being collected, current recommendations should be followed.

Direct, local changes in the expression of ACE and ACE2 in the myocardium of patients with COVID-19 may also cause cardiac lesions. That was shown during the 2003 epidemic caused by a similar virus, SARS-CoV-1 [45]. Data from a small study of patients with confirmed COVID-19 showed increased levels of angiotensin II [11]. It should be kept in mind that a decrease in ACE2 and an increase in angiotensin II can potentially cause deterioration in patients due to cardiovascular damage. Thus, it can be suggested that the administration of ACE inhibitors and ARBs to patients with COVID-19 can be seen not only as protection against lung damage, but also as prevention of cardiac lesions in patients with cardiovascular indications for their use. The possibility of preventing complications in patients with COVID-19 by using losartan in patients who have not previously taken ACE inhibitors or ARBs is also being studied.

Conclusion

The analysis of mechanisms of cell penetration by SARS-CoV-2 does not provide conclusive answers to the question of

whether the use of ACE inhibitors and ARBs could harm patients with COVID-19 and/or increase the risk of infection by this virus. Available data rather suggest that the use of ACE inhibitors and ARBs may reduce the risk of lung and heart lesions in patients with COVID-19, including elderly patients with comorbidities. It should be borne in mind that all assumptions are based on the analysis of mechanisms of action and experimental studies and to a lesser extent on clinical data. Given these points, the viewpoint of the world scientific communities is now that there is no basis to either withdraw these drugs or to intentionally administer them to treat COVID-19 [44, 46, 47]. However, there is still hope for efficacious inhibition of RAAS in patients with COVID-19.

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