Why not change the therapy of hypertension in patients with COVID-19. Dual role of angiotensin-converting enzyme 2

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Abstract

Despite many organizational and medical efforts, the COVID-19 epidemic continues and is taking a lethal toll. Preliminary reports have already reported that the mortality associated with this disease is much higher in people with comorbidities, including hypertension. SARS-CoV-2 virus enters the body through the receptor which is the angiotensin converting enzyme 2 (ACE2). The administration of angiotensin converting enzyme inhibitors or sartans increases the activity of this enzyme. Therefore, there was a suspicion that patients treated with these preparations become more easily infected, and the infection itself is more severe and is associated with greater mortality. On the other hand, the ACE2 enzyme is known to reduce the risk of lung damage. The paper presents current reports describing the frequency of SARS-CoV-2 virus infection in patients with hypertension, the course of infection and the effect of administration of ACE inhibitors and sartans on the mortality of these patients. The presented data indicate that the use of angiotensin converting enzyme inhibitors and sartans in patients with COVID-19 does not worsen the course of the disease, and according to some authors this treatment even reduces the mortality of this infection.

Key words: COVID-19; hypertension; angiotensin-converting inhibitors and sartans; angiotensin-converting enzyme 2

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Introduction

The whole world is currently suffering from the COVID-19 epidemic caused by the SARS-CoV-2 virus. The epidemic started in China at the end of December 2019 and then moved to Europe, the United States and over 180 countries around the world. In November 2020, more than 50 million people were infected with the virus and more than 1 200 000 patients died. Deaths are most often caused by acute respiratory failure, less often by heart failure or multi-organ failure, and usually involve older people with comorbidities. There have been reports in the press as well as in scientific publications that hypertension favors SARS-CoV-2 infection and significantly worsens its prognosis [1]. In addition, there have been warnings that not all hypertensive drugs can be safely used in patients with COVID-19 [2, 3]. Therefore, the question arises whether, in the light of recent studies, hypertensive patients are more likely to be infected with SARS-CoV-2, whether the course of the infection in hypertensive patients

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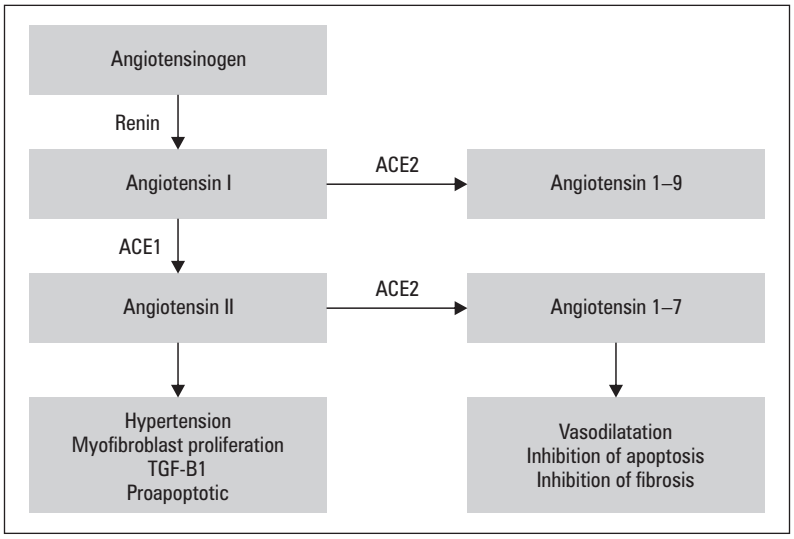

Figure 1. Diagram of renin–angiotensin and aldosterone system and its effects on the circulatory and pulmonary systems.
ACE — angiotensin-converting enzyme; TGF-B1 — transforming growth factor-B1

has a significantly worse prognosis and, finally, what should be the hypertension therapy for patients with COVID-19?

The renin-angiotensin-aldosterone system plays an important role in the pathogenesis of SARS-CoV-2 infection. The first-converting enzyme (ACE1) converts angiotensin 1 and then angiotensin 2. The second-converting enzyme (ACE2) converts angiotensin 1 to angiotensin 1–9 and then to angiotensin 1–7 (Fig. 1).

Recently, SARS-CoV-2 has been shown to penetrate the body through the angiotensin-2-converting enzyme (ACE2) [4, 5]. The presence of the ACE2 enzyme has been demonstrated in many tissues, namely the alveoli, heart, kidneys, testicles, and adipose tissue, and a small amount of this enzyme dissolves in circulating blood and is not bound to tissues [6]. Most of this ACE2 enzyme has been shown to be associated with type II pneumocytes of the alveoli located very close to the capillaries of the pulmonary artery. These cells are responsible for the synthesis of surfactant, which facilitates gas exchange [7]. The virus enters the alveoli most easily during inhalation, multiplies here and causes the known clinical symptoms of COVID-19 such as coughing, dyspnea and fever. Studies of the coronavirus that caused SARS in 2002–2003 have shown that this virus with a slightly lower infectivity but causing higher mortality also penetrated the body via the ACE2 enzyme. In experimental animals genetically deprived of the ACE2 enzyme after exposure to SARS, the amount of SARS in lung tissue was 100 000 times lower than in animals with normal ACE2 activity [8]. The combination of the virus with the ACE2 receptor reduces the activity of this enzyme and then ACE1 increases the concentration of angiotensin II [9]. Mortality in infected patients (not including asymptomatic patients) is high, ranging from 5.6 to 15.2%, and is higher in the elderly and men [10].

Stimulation of the renin–angiotensin–aldosterone system plays an important role in acute respiratory failure. High concentration of angiotensin II not only causes hypertension but also has a negative effect on the respiratory system [11]. This compound has been shown to stimulate growth factors [transforming growth factor-B1 (TGF-B1) and connective tissue growth factor (CTGF)], which accelerate fibroblast proliferation in pulmonary tissue and increased synthesis of type I collagen, cause vasoconstriction of pulmonary vessels, and cause oxidative stress. All these factors accelerate pulmonary tissue fibrosis. The action of angiotensin II accelerates apoptosis of alveolar epithelium. The opposite effect is shown by angiotensin 1–7 produced by ACE2 [12–14]. It inhibits the apoptosis of alveolar epithelial cells and acts antifibrinolytically. This has been shown in mouse experiments, among others, that ACE2 plays an important protective role and reduces the symptoms of acute pulmonary failure. In experimental animals, acute endotoxin-induced lung injury was triggered and sepsis-related lung injury was studied. In those animals that were deprived of the ACE2 gene (ACE2 KO), the symptoms of acute lung failure increased faster, increased blood vessel permeability and inflammatory cell infiltration appeared. Pulmonary edema was increasing [15]. Subsequent studies have confirmed that the administration of recombinant ACE2 at a dose of 400 μg/kg to dormant and

underoxygenated animals resulted in a decrease in pulmonary artery pressure, and partial oxygen pressure increased significantly [16]. The expression of ACE2 is greater in young people and women [17].

Zambelli et al. induced acute respiratory distress syndrome (ARDS) in rats by inhalation of hydrochloric acid [12]. Angiotensin 1–7 infusion of 300 µ/kg/day reduced white blood cells in bronchial lavage (BAL) — and significantly increased oxygenation (PaO_2/FiO_2). Prolonged administration of angiotensin 1–7 prevented lung fibrosis which appears after ARDS. Similar conclusions were reached by Imai et al., who demonstrated the protective effect of recombinant ACE2 on the development of acute lung failure in mice [14]. In these mice they caused acute lung injury. In those animals that had previously received an infusion of angiotensin 1–7, the inflammatory lesions of lung tissue were much smaller. Therefore, ACE2 plays two opposing roles. On the one hand, it allows the SARS-Cov-2 virus to penetrate the body, and on the other hand, it protects against lung tissue injury. The results of experimental studies have encouraged attempts to administer recombinant ACE 2 in people with pneumonia, especially in the course of ARDS so often leading to death, and in patients with COVID-19. So far, only one study has been presented in which recombinant ACE2 infusion was administered intravenously to patients with ARDS [18]. The administered compound turned out to be safe, caused an increase in angiotensin 1–7 and surfactant and a tendency to reduce interleukin 6. However, no reduction in the symptoms of acute lung injury was shown, and in particular, the value of PaO_2/FiO_2 did not change. In order to evaluate the effectiveness of recombinant ACE2 treatment in SARS-infected patients, a pilot clinical trial was started, code-named NCT 0428768. The high value of the ratio of angiotensin II (ACE2/angiotensin II) also reduces the risk of developing heart failure and prolongs the life of patients with this disease [19]. Research results show that the ACE2 enzyme plays two roles in SARS-CoV-2 infection: this enzyme is necessary for infection with this virus; on the other hand, the low activity of this enzyme in lung injury contributes to the rapid progression of the disease. Is hypertension, in the light of recent studies, more common in patients with COVID-19 than in the general population?

According to preliminary studies, arterial hypertension is one of the common so-called coexisting diseases (as well as chronic obstructive pulmonary disease, diabetes, cancer) in coronavirus-infected patients. First of all, it is worth considering how frequent are the co-existing diseases in the population not infected with the SARS virus. In the United States, after examining more than 440 000 adults, it turned out that 45.5% of people have at least one of the abovementioned diseases [20]. In 28% of the subjects it was one disease, in 12% two diseases, in 4.7 subjects 3 diseases and in 2% of them 4 or more diseases were found to coexist. As a single condition, hypertension was the most common (32.4%). In 19.8% of young people, at least one disease was reported, and in 80.7% of people aged 80 and over.

The frequency of hypertension in people with COVID-19 was evaluated in two recently published meta-analyses. In the first one, by Yang et al., the frequency of hypertension in infected individuals is 21.1% [21]. According to the second meta-analysis performed by Emami, the prevalence of hypertension in this group of patients is lower (16.3%) [22]. The frequency of hypertension in patients infected with SARS-CoV-2 is therefore low. The majority of patients included in the above analysis were in China and Iran. According to a recent epidemiological study, the prevalence of hypertension in the Chinese population is 23.2% [23]. According to the Mancia et al.'s study, also in Europe, the prevalence of hypertension accompanying the coronavirus infection does not differ significantly from that of the whole population [24]. The incidence of hypertension is much higher in elderly patients. For example, in the Garg and Kim's study, 74.5% of patients with COVID-19 were over 50 years old and the prevalence of arterial hypertension in this age group was 49.7%, obesity 48.3%, chronic lung disease 34.6%, diabetes 28.3%, and cardiovascular disease 27.8% [25]. Here too, the prevalence of hypertension in this age group in patients with coronavirus infection does not differ from the prevalence of hypertension in the general population.

However, COVID-19 patients, according to many previously published papers, suffer from this disease much more severely if accompanied by hypertension [26–30]. Only two authors have not found a more severe course of this infection despite the coexistence of hypertension. This is confirmed by meta-analyses of Yang et al. [31] and Wang et al. [32], Lippi et al. [33]. The Yang's study shows that the severe course of this disease is more than 2 times (2.36) more frequent than that of people with normal blood pressure. Meta-analysis by Wang et al. shows that hypertension is an independent risk factor for severe COVID-19 and the OR is 2.29 ($p < 0.001$) [32]. Hypertension is the most common but not the most dangerous risk factor, as other co-morbidities increase the risk of severe infection even more. Diabetes mellitus more than doubles

the risk (OR = 2.47, p < 0.001), chronic obstructive pulmonary disease increases it almost six times (OR = 5.97, p < 0.01), cardiac diseases almost three times (OR = 2.93, p < 0.01) and cerebrovascular diseases almost four times (OR = 3.89, p < 0.002) [32].

The Italian authors, on the basis of 13 studies covering 2893 people infected with SARS-CV-2, estimated that coexisting arterial hypertension significantly increases the risk of severe disease by almost 2.5 times (OR = 2.49). Similarly, the risk of mortality in patients with hypertension and COVID-19 increases more than twice (OR = 2.42) [33]. In metaregression, the authors have shown a significant correlation between the age of patients and the severity of the course of infection and coexistence of hypertension (p = 0.03). In the discussion of their work, the authors draw attention to the fact that elderly people are often accompanied by other coexisting diseases and that old age itself may be associated with reduced immunity. According to other studies from China, not only severe course but also mortality in the course of COVID-19 is much higher if the infection is accompanied by hypertension. According to many authors, however, the mortality rate in elderly patients with COVID-19 was highest [34]. Therefore, a number of authors question the very negative effect of hypertension on prognosis in patients with COVID-19, believing that the determining factor is the elderly patients' age and not hypertension itself [35]. To answer this question, mortality in this infection should be assessed in patients with concurrent hypertension as well as in patients with normal blood pressure in young and elderly people. So far, we do not have a large study dedicated to this issue. Only one study by Guan et al. in relatively younger patients determined the effect of hypertension on the prognosis of patients with COVID-19 [36]. The average age of patients was relatively low, i.e. 48.9 years and 42.7% were women. In 16% of the subjects the disease was severe. In 21.1% at least one concurrent disease was found. The most frequent disease accompanying the infection was arterial hypertension (16.9% followed by diabetes mellitus 8.2%). After taking into account the disruptive factors such as age, cigarette smoking, risk factors for the severe course of the disease were arterial hypertension (HR = 1.58), the presence of chronic obstructive pulmonary disease (HR = 2.68), diabetes (HR = 1.59), and malignancies (HR = 3.5). The presence of two concomitant diseases increased the risk of severe course of the infection more than twice (HR = 2.59) and one concomitant disease by 80% (HR = 1.79). This study shows that arterial hypertension in relatively young people increases the risk of severe disease to a lesser extent than in older people.

The presence of SARS-CoV-2 RNA in the system of infected persons is usually found from 13 to 22 days (17 days on average) after the onset of COVID-19 symptoms. Longer presence of the virus in the system of patients extends their stay in hospital. More frequent virus presence over 15 days is found in men (p = 0.009), elderly people (p = 0.033), co-morbid hypertension (p = 0.001), delayed admission to hospital (p = 0.001), severe condition on admission (p = 0, 049), in patients treated with respirators (p = 0.006) and in patients treated with steroids (p = 0.025). Patients with a longer presence of the virus have a longer period of fever, slower absorption of inflammatory changes in the lungs than patients with a faster clearance of the virus [37]. The last two studies cited argue that not only age but also the co-existence of hypertension may to some extent worsen the prognosis in patients with SARS-CoV-2. Only subsequent studies evaluating not solely the presence of hypertension itself but also its severity and the co-existence of further concomitant diseases may ultimately determine whether hypertension significantly worsens the prognosis and mortality of SARS-infected patients regardless of their age.

Patients with hypertension are often treated with angiotensin-converting enzyme 1 inhibitors or sartans. According to some authors, administration of these drugs increases the concentration of angiotensin converting enzyme 2 (ACE2) [38]. Since the SARS-CoV-2 virus enters the body via ACE2, it could be suspected that patients with hypertension treated with these drugs would become more frequently infected with the virus. This is the position taken by Cure et al. [2]. The meta-analyses cited above concerning the prevalence of hypertension in patients with COVID-19 did not confirm this suggestion. However, some authors suspect that therapy with angiotensin converting enzyme inhibitors or sartans leads to worse prognosis in this disease and suggest that these drugs should be discontinued in patients infected with SARS-CoV-2.

In recent years several studies have evaluated the influence of ACE1 inhibitors or sartans on ACE2 activity in animals, and in individual human studies. The results of these studies were divergent. Burchill et al. did not observe changes in ACE2 expression in rat hearts following administration of ramipil or valsartan [39]. However, in most animal studies, an increase in ACE2 activity was observed after administration of these drugs. Ferrario et al. observed a 4.7-fold increase in ACE2 in rats after administration of lisinopril and a 2.8-fold increase in ACE2 after administration of losartan [38]. There are no studies on the effect of angiotensin converting en-

zyme inhibitors or sartans on ACE2 activity in pulmonary tissue. Experimental studies have attempted to assess whether ACE1 inhibitors or sartans will reduce the symptoms of pneumonia. Shan et al. observed that the administration of losartan reduced the risk of developing acute lung injury during sepsis in experimental mice, and significantly improved their survival [40]. The administration of angiotensin converting enzyme inhibitors or sartans has also been shown to be beneficial in humans in many bacterial or viral lung injuries and reduced mortality in already developed pneumonia. Chin-Cheng Lai et al. compared the effect of treatment with angiotensin converting enzyme inhibitors or sartans on the risk of exacerbation of the disease or pneumonia occurrence in patients with chronic obstructive pulmonary disease [41]. Over 12 000 patients with chronic obstructive pulmonary disease were divided into 2 subgroups of approximately 6000. One group of patients had been receiving an angiotensin converting enzyme inhibitor for over 90 day; the other group was treated with sartans for a similar period of time. Patients treated with sartans had a 19% lower risk of severe exacerbation of chronic obstructive pulmonary disease than patients treated with angiotensin converting enzyme inhibitors. The influence of these drugs on the course of pneumonia in the elderly was studied by Spannella et al. [42]. Among 310 patients aged 88 ± 5.1 years admitted to hospital due to pneumonia, the use of these drugs was associated with significantly lower mortality in the multivariate analysis, which included the age of the patients, hemoglobin concentration, NT-proBNP level, and the degree of kidney injury. The authors observed no difference in the number of deaths in patients treated with sartans or angiotensin converting enzyme inhibitors. In 2012, a meta-analysis by Caldeira et al. was published showing that the use of angiotensin converting enzyme inhibitors significantly reduces the risk of pneumonia by 34%, and the use of sartans by 31% in people at risk of developing this disease (chronic lung diseases, heart disease, smokers, kidney failure) [43]. Uncontrolled arterial hypertension leads to dysregulation of the immune system. Primary arterial hypertension showed an increased lymphocytes count [44] and dysfunction of CD8 + T cells [45]. Such a disturbed immune system is less able to cope with viral infection. Effective treatment of hypertension with, inter alia, angiotensin converting enzyme inhibitors and sartans can strengthen the immune system [46]. Treatment with angiotensin converting enzyme inhibitors and statins also reduced mortality from viral pneumonia. A retrospective analysis by Henry C. et al. of over 500 patients with viral pneumonia showed that the use of angiotensin converting enzyme inhibitors or statins statistically significantly reduced mortality or the need for intubation by as much as 75% [47].

The data presented above represent the state of knowledge at the time of the outbreak of the coronavirus epidemic. As already mentioned during this period, two views on the administration of angiotensin converting enzyme inhibitors in hypertensive patients infected with SARS-CoV-2 virus were clashing. One, indicating an increase in ACE2 after the administration of these drugs, which could lead to an increased amount of viruses associated with this enzyme and penetrating the system, and another opinion about the beneficial effects of converting enzyme inhibitors and sartans on lung inflammation.

We already have several studies assessing the impact of these drugs in patients with hypertension during coronavirus infection. The first study was conducted by the Chinese, who recruited 1128 patients with COVID and hypertension [48]. These patients came from hospitals in Hubei Province and were recruited for the study from December 31, 2019 to February 2020. From this group, 188 patients aged 55–68 (64 years on average) treated with angiotensin converting enzyme inhibitors or sartans were selected. The remaining 940 patients aged 57–69 (64 years on average) did not receive the abovementioned drugs despite high blood pressure. The mortality rate in the first group was 3.7%, in the second group 9.8% ($p = 0.01$). After taking into account age, gender, concomitant diseases and hospital treatment, the overall mortality rate in patients treated with angiotensin converting enzyme inhibitors or sartans was significantly lower (HR = 0.42, $p = 0.03$) compared to patients not receiving these drugs. In addition, when hypertension therapy with drugs other than converting enzyme inhibitors and sartans was included, HR was 0.30 ($p = 0.01$) in favor of treatment with the latter. Different results were obtained by Li et al. [49]. In this retrospective one-hospital study (Central Hospital of Wuhan), 1178 patients with COVID-19 were observed. The overall mortality rate of these patients was high, i.e. 11%. From this group of patients, 362 patients with hypertension at an average age of 66 years were identified, of whom 115 were treated with angiotensin converting enzyme inhibitors and the remaining patients did not receive these drugs despite their hypertension. In this group of hypertensive patients, the mortality rate was 21.3% and did not differ between the subgroups treated and those not treated with angiotensin converting enzyme inhibitor or sartan. The above results suggest that therapy with angiotensin

converting enzyme inhibitors and sartans does not worsen the course of the disease, and perhaps even slightly improves the prognosis. A large study on this issue recently published (May 1, 2020) included 6272 patients in medium or severe condition due to SARS-CoV-2 infection treated in Italy [50]. The control group consisted of 30 759 patients matched by age and gender. The average age of the subjects was 68 ± 13 years. The use of angiotensin converting enzyme inhibitors or sartans due to hypertension or heart disease was slightly more common in patients with COVID-19 than in the control group where the frequency of cardiovascular diseases was slightly lower. The frequency of severe infection in patients with hypertension treated with angiotensin converting enzyme inhibitors or sartans did not differ significantly from that in patients treated with other hypotensive drugs such as diuretics or calcium antagonists. The authors of this study confirm the previous position of the recommendations of the Polish and European Society of Hypertension not to discontinue the discussed drugs in patients with hypertension infected with coronavirus.

A meta-analysis by Zhang et al. covering 190 000 patients with COVID-19 described in 12 scientific papers has been published recently [51]. The results of this meta-analysis clearly showed that the use of angiotensin converting enzyme inhibitors or sartans only statistically insignificantly reduced the number of patients with severe infection with the SARS-CoV-2 enzyme ($p = 0.111$). However, the analysis of the mortality of the studied patients showed that that the use of these drugs significantly reduced the percentage of deaths (OR = 0.45, $p = 0.006$) compared with patients with hypertension not using these drugs. Guo et al. published a meta-analysis on the effect of angiotensin converting enzyme inhibitors and sartans in patients with COVID-19 [52]. In this study, the cited authors showed that the use of these drugs in patients with concomitant arterial hypertension reduces the severity of the disease, with borderline statistical significance ($p = 0.11$), and at the same time statistically significantly reduces mortality ($p = 0.004$). Subsequent meta-analyzes do not bring a final decision whether the use of angiotensin converting enzyme inhibitors and sartans improves the prognosis and reduces mortality in patients with hypertension infected with SARS virus. In a meta-analysis by Flacco et al. the use of these drugs is statistically insignificant and slightly improves the prognosis of patients with COVID-19 [53]. The results of the meta-analysis of Greco et al. are similar. ACE inhibitors and sartans can be safely used in patients with arterial hypertension and COVID-19 but they do not improve the prognosis of these patients [54]. According to the meta-analysis of Pranata et al., the use of angiotensin converting enzyme inhibitors has no effect on the mortality of hypertensive patients infected with SARS virus, while the use of sartans significantly reduces the mortality in these patients (OR = 0.51, $p = 0.02$) [55]. Angiotensin converting enzyme inhibitors and sartans, according to the meta-analysis of Pirola and Sookoian, have a beneficial effect on the prognosis of patients with COVID-19 [56]. In the largest meta-analysis by Baral et al. including 28 872 patients with arterial hypertension and COVID-19, the use of these drugs significantly reduces both the severe course of the disease and mortality (OR = 0.664, $p = 0.031$) [57]. The results of the meta-analysis by Patoulias et al. in September 2021 are surprising and contrary to the findings reported so far [58]. According to this meta-analysis, administration of ACE inhibitors or sartans in patients with arterial hypertension and COVID-19 significantly reduces the risk in Asian countries (OR = 0.37), while increasing the risk of severe disease in the United States and Europe (OR = 1.75) [58].

The vast majority of the above data suggests that patients with arterial hypertension and COVID-19 should continue to use all existing antihypertensive drugs, including angiotensin converting enzyme inhibitors or sartans. According to some authors, it is also recommended to use spironolactans, which have also been shown to significantly increase the level of the ACE2 enzyme and are effective form of treatment for ARDS [59]. Hypopotassemia is present in a significant proportion of patients with COVID-19. These electrolyte disturbances correlate with the severe course of COVID. The use of sartans, carvedilol and eplerenone increases the serum level of potassium and may thus reduce the course of coronavirus infection [60]. It is also advisable to use statins because, according to Zhang, their use will reduce the mortality rate in patients with COVID-19 [61].

The above current literature review reflects the prevailing belief that the renin-angiotensin-aldosterone system affects the frequency and course of coronavirus infections. A large randomized clinical trial is needed to finally elucidate the role of angiotensin converting enzyme inhibitors and sartans in the treatment of COVID-19.

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