Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Review

J Hypertens Res (2020) 6(4):117-121

Hypertension and chronic obstructive pulmonary disease – current challenges during the COVID-19 pandemic

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Received: October 23, 2020, Accepted: December 3, 2020

Abstract

Hypertension and chronic obstructive pulmonary disease are common conditions in the adult population that have a significant impact on the quality of life, morbidity, and mortality. The SARS-CoV-2 infection has worsened the prognosis of these patients and has complicated their therapy. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) as its receptor and disturbs the renin-angiotensin system in the lungs and other organs. Patients with hypertension and cardiovascular disease have an increased risk of severe COVID-19, and some data suggested that ACE inhibitors and angiotensin receptor blockers could increase this risk. Also, the benefits of inhaled corticosteroids in chronic lung disease have been challenged.

Keywords: Comorbidities, prognosis, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, SARS-CoV-2.

Introduction

High blood pressure (BP) is the major cardiovascular risk factor found in the adult population. Worldwide, the number of patients with high blood pressure reached 1.13 billion in 2015, which represents 30-45% of the total population. Prevalence increases with age, reaching 60% after the age of 60 years. The number of patients with hypertension will increase by 10-15% by 2025. Untreated hypertension increases the risk for cardiovascular complications (myocardial infarction, stroke, death), atrial fibrillation, cognitive decline, and dementia. Hypertension is underdiagnosed, with only 40% of patients being prescribed medication, and only 35% of these reach the therapeutic targets [1]. Chronic obstructive pulmonary disease (COPD) is also underdiagnosed in the adult population. It reduces the quality of life, increases hospitalization and mortality rates. The prevalence of COPD in Romania in 2018 was 2.23%, and estimations for the future indicate an ascending trend [2]. Most patients with COPD (86%) have at least one addi-

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tional comorbidity, and 22.3% of patients with pulmonary diseases have more than five comorbidities. Frequent comorbidities are hypertension (in 35.3-52% of cases), coronary artery disease (in 20.8%), heart failure, peripheral arterial disease, chronic hepatitis, psychiatric diseases [3].

The economic impact of treating hypertension, COPD, and their complications is significant, and even more so in the current pandemic context. Patients with hypertension and COPD are highly susceptible to develop severe COVID-19. The reason for this predisposition is probably multifactorial, and there is data indicating that some classes of antihypertensive drugs could increase the risk. Our paper presents data about the COVID-19 risk in patients with hypertension and COPD and its impact on their treatment.

SARS-CoV-2 and its connection with the renin-angiotensin-aldosterone system

The first cases of the new coronavirus-induced infection or COVID-19 occurred at the end of 2019 in Wuhan, China. The disease is caused by a new coronavirus that causes severe acute respiratory syndrome (SARS-CoV-2). The first cases were workers in seafood markets who got the infection from bats, the usual reservoir hosts. SARS-CoV-2 genome is 96.2% similar to batCoVRa TG13 [4]. The infection spread worldwide, affecting 59 million people by November 2020, with 1.41 million deaths in 220 countries [5].

SARS-CoV-2 is an enveloped, non-segmented, positive-sense RNA virus, included in the orthocoronavirinae subfamily [4]. The virus has a diameter of 65-125 nm [4]. In human cells, SARS-CoV-2 interacts with the angiotensin-converting enzyme 2 (ACE2) receptor, which is present on the cell membranes of many organs (blood vessels, heart, lungs, nervous system, intestines, kidneys). ACE2 is expressed on endothelial cells, on vascular smooth muscle cells, on epithelial alveolar cells type I and II, to a lesser amount on bronchial epithelial cells, on brush border cells from the proximal convoluted tube, and glomerular epithelial cells [6]. The spike protein (S) arranged in homotrimers, a component of the virus membrane, interacts with ACE2 and transmembrane serine protease called TMPRSS2 [7, 8]. This protease is necessary for S protein priming (S protein cleavage at the S1/S2 and at the S2' site) [7]. The S2 subunit drives the fusion of viral and cellular membranes. The virus and ACE2 are internalized, then the virus detaches from its receptor and triggers viral protein and RNA synthesis. A TMPRSS2 inhibitor can block virus entry [7]. SARS-CoV-2 also uses other cell receptors like CD209 (expressed on macrophages, heart, vessels) and C-type lectin [6, 8].

ACE2 is a zinc metallopeptidase with 805 amino acids, which shares a 40% similarity with ACE [6]. The physiological role of ACE2 is to hydrolyze angiotensin II (Ang II) in Ang (1-7). ACE2 also hydrolyzes Ang I in Ang (1-9), but the affinity for Ang I is lower. Ang (1-7) causes vasodilation and has anti-proliferative, anti-inflammatory, and antioxidant effects. ACE2 and Ang (1-7) represent the primary counterregulatory system for Ang II [6]. To further complicate the interaction, Ang II through AT1 receptor can trigger ACE2 internalization and degradation in lysosomes [9].

The viral infection leads to ACE2 internalization, decreases Ang (1-7) synthesis, and increases Ang II concentration. Ang II promotes vasoconstriction, triggers inflammation, increases ROS (reactive oxygen species synthesis), endothelial dysfunction, and causes lung injury. In severe COVID-19 cases, Ang II has a high concentration in lung tissue [6-8].

There is a controversy over the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) in patients with COVID-19. In animal models, ACEI/ARB increase ACE2 expression on the cell surface and could theoretically increase susceptibility to virus entry. In an animal study, rats that were treated with lisinopril had an increased level of ACE2 mRNA in heart cells, but its activity was not increased. After losartan administration, both ACE2 mRNA levels and the enzyme's activity were increased in cardiac cells [10]. In another study, the authors found no difference between blood ACE2 activity in patients who were treated with ACEI/ARB versus those who were not taking these drugs. Urinary concentration of ACE2 was higher in patients treated with olmesartan. Other ARBs did not change ACE2 urinary concentration [11]. There is not enough information to conclude that ACEI/ARB change ACE2 expression on cell membranes, in particular in lung tissue.

Do hypertension and antihypertensive drugs increase the risk of COVID-19?

Epidemiological data from a large study that included 5700 patients with COVID-19 from New York City and surroundings found that a significant proportion of patients had cardiovascular risk factors or overt disease. Over half of cases (56.6%) had hypertension, followed by obesity in 41.7% of cases, diabetes in 33.8%, coronary heart disease in 11.1%, and heart failure in 6.9% of cases. The prevalence of risk factors was higher than in the general population. The same pathologies increase the risk of severe COVID-19 [8, 12]. The presence of cardiovascular disease increases up to 5 times the mortality in COVID-19, which can reach 10.5% [8, 13]. Fatality increases with age, starting from a low level in patients younger than 30 years, increasing to 3.5% in

patients aged 60-69 years and 20% after 80 years [8]. Aging increases the number of comorbidities, including cardiovascular disease.

Modern antihypertensive therapy includes several classes of drugs that reduce cardiovascular complications. ACEI and ARB are widely used in treating hypertension because of efficient control of BP values, reverse remodeling of hypertension mediated organ damage, and few adverse effects. They improve left ventricular function, reduce mortality and hospitalization rates in heart failure and after myocardial infarction. They also slow the decline in kidney function in patients with diabetes mellitus. Clinical trials support a neutral effect of ACEI/ARB on the risk of SARS-CoV-2 infection and the risk of developing a severe form of the disease [8]. The results of some relevant trials are presented below. A study by Fosbøl and colleagues analyzed the prognosis of patients with COVID-19 with previous ACEI/ARB therapy and the susceptibility of hypertensive patients to get the infection [14]. The prognostic arm followed 4480 patients with COVID-19 admitted to hospital between February - May 2020 in Denmark. The mean age was 54.7 years, and 48% of patients were males, and 20% were receiving ACEI/ARB therapy. During the 30-day follow-up, the mortality rate was 18.1% in the group receiving ACEI/ARB versus 7.3% in those without ACEI/ARB. The endpoint of death or severe COVID-19 was found in 31.9% of cases in the ACEI/ARB group versus 14.2% in the other group. However, the raw data did not account for differences in age, sex, and comorbidities between groups. Patients in the ACEI/ARB group were older than patients without therapy (72.8 years versus 50 years), more often had hypertension (70.8% versus 5.8%), diabetes mellitus (24.2% versus 5.4%) or other comorbidities (myocardial infarction 21.6% versus 5.2%, heart failure 14.6% versus 3.1%). The ACEI/ARB group also included more patients with cancer, cerebrovascular disease, chronic kidney disease, or COPD. After multivariate adjustment including age, sex, comorbidities, there was no significant difference in the risk of death (HR=0.8395% CI, 0.67-1.03]) or severe COVID between groups (HR=1.04 95% [CI, 0.89-1.23]). There was no difference between ACEI/ARB and calcium channel blockers-treated patients (HR=0.94). The susceptibility arm compared 571 patients with hypertension and COVID-19 with 5710 hypertensive patients (age and sex-matched) without infection. ACEI/ARB therapy was used in a similar proportion (86.5% and 85.4%). The HR for infection was 1.05 [14].

Similar results were reported by Zhang from a group of 1128 patients with COVID-19 and hypertension. 16.6% of patients were receiving ACEI/ARB therapy. After multivariate adjustment, HR for mortality was 0.42 (0.19-0.92) in the ACEI group [15].

In Abajo's trial, common risk factors (hypertension, diabetes, dyslipidemia) increased the risk of severe viral infection 1.46 times, while the presence of cardiovascular disease increased the risk 1.98 times [16]. The risk of hospitalization is increased by 1.71 times in patients with ACEI/ARB therapy and 1.82 times in those receiving other classes of antihypertensive medication. If the use of other antihypertensive medication classes is considered a reference, then inhibitors of the renin-angiotensin system have an HR of 0.94 for patient hospitalization. The risk is similar for ACEI and ARB (HR of 0.8 and 1.1). The duration of therapy did not change the risk [16].

Discontinuation of ACEI/ARB therapy can deteriorate the hemodynamic status and is not recommended in COVID-19 patients. The European Society of Cardiology recommends continuing the therapy with these classes of drugs [8].

COPD patients have an increased risk of developing severe COVID-19

The prevalence of COPD among patients hospitalized for COVID-19 varies between 0-14% in different parts of the world and does not differ from the background rate of the pulmonary disease [17]. The prevalence of COPD among severe COVID cases admitted to the intensive care unit (ICU) varies from 4% to 38% [17]. In China, patients with COPD had an odds ratio of 2.68 for admission to ICU, need for mechanical ventilation, or death compared with patients without a preexisting pulmonary disease [18]. COPD patients and current smokers have a higher ACE2 expression on bronchial epithelial cells compared with control cases, which could increase their susceptibility to infection [17]. Information regarding the effects of inhaled corticosteroids (IC) is controversial. Peters *et al.* showed that IC reduce ACE2 expression on bronchial epithelial cells, which could decrease virus entry [19]. A recent study suggested a potential harm induced by IC. Schultze analyzed data from a large number of patients with pulmonary disease (148577 patients with COPD and 818490 patients with asthma) who were receiving chronic inhaled therapy. Patients taking IC had a higher risk of death due to COVID-19 than those taking long-acting beta-1 agonists (adjusted HR=1.39) [20]. In asthma patients, which used higher doses of IC, had a higher risk of death (HR=1.55) compared with those taking short-acting beta-agonists, while small and medium doses of IC did not increase the risk (HR=1.14) [20]. The author explained that differences in the severity of chronic pulmonary disease might have influenced the result. IC are known to increase the risk of bacterial pneumonia, but whether this is true for SARS-CoV2 is not clear. On the other hand, intravenous dexamethasone had beneficial effects and reduced mortality in patients with moderate and

severe COVID-19. The current recommendation is that inhaled medication should be continued in the usual doses in patients with lung disease [20].

Recommendations for the treatment of hypertension in COPD patients

Hypertension therapy generally includes changes in diet, smoking cessation, and blood pressure-lowering drugs. Guidelines recommend using combination therapy from the beginning, for example, an ACEI or ARB together with a calcium channel blocker or a diuretic. Combination therapy is more efficient than monotherapy in reaching BP targets, with fewer adverse effects and increased adherence, when the combination is available in a single pill. If BP is not under control, then triple therapy with an ACEI or ARB plus calcium channel blocker plus thiazide or a thiazide-like diuretic is recommended [1]. Dosages can be increased. In the third step, one can add an aldosterone receptor antagonist or a beta-blocker, or an alfa receptor blocker. A beta-blocker can be used from the first step when specific comorbidities are present (heart failure, angina, myocardial infarction, atrial fibrillation) [1]. Beta-blockers (selective beta1) are generally well tolerated in COPD patients, but they can worsen lung function and reduce the efficacy of inhaled bronchodilators [1]. Choosing between ACEI and ARB is difficult. According to Messerli, their effect is similar in reducing cardiac death, stroke, and myocardial infarction or in slowing deterioration of kidney function [21]. ACE inhibitors more often cause adverse effects [21]. Cough occurs more often during ACEI than during ARB therapy (10.6% versus 3.5%) [22]. Cough, angioedema, and bronchospasm are caused by high bradykinin levels induced by ACEI.

ACEI and ARBs affect the prognosis of COPD patients differently. ACEI can increase mortality by 33%, the risk of pneumonia by 22%, the risk of worsening of lung disease by 19%, as well as the risk of hospital admission by 24% versus ARBs. The beneficial effects of ARB can be due to the activation of the ACE2/AT2R/Mas pathway, which reduces lung inflammation [23]. Similarly, in Paulin's study, ARBs reduced mortality in COPD patients by 37% [28]. Calcium channel blockers also reduce mortality by 14% [25]. According to this data, ARBs are the preferred therapy in COPD patients.

Conclusions

Hypertension and COPD are common diseases that increase the risk of severe SARS-CoV2 infection. This viral infection disturbs the renin-angiotensin system and its counterregulatory arm (ACE2 – Ang (1-7)), leading to increased Ang II concentration that causes lung injury. ACE inhibitors and angiotensin receptor blockers do not increase the risk of SARS-CoV-2 infection in patients with preexisting cardiovascular disease and do not increase mortality compared with other classes of antihypertensive medication. Stopping ACE inhibitors or ARBs can have severe consequences and is not recommended. ARBs improve the prognosis of COPD patients and are preferred to ACEI.

Conflict of Interest

The author confirms that there are no conflicts of interest.

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