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COURSE AND THERAPY OF ARTERIAL HYPERTENSION IN PATIENTS WITH COVID-19

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Annotation
A number of publications regarding the course of COVID-19 infection and its relation to comorbidities have appeared since December 2019, when the first cases of atypical pneumonia were diagnosed in China. There is evidence of the higher susceptibility and higher risk of unfavourable outcomes in comorbid patients, including those with hypertension. We summarize the available data on the association with the COVID-19 infection and arterial hypertension, and discuss potential risks, e.g. the risks and benefits of antihypertensive therapy (in particular, related to the blockers of renin-angiotensin-aldosterone system) and the management approaches.

Key words: coronavirus, COVID-19, SARS-CoV-2, hypertension, cardiovascular risk, renin-angiotensin-aldosterone blockers, angiotensin-converting enzyme inhibitors 2, zinc.

ТЕЧЕНИЕ И ТЕРАПИЯ АРТЕРИАЛЬНОЙ ГИПЕРТОНИИ У БОЛЬНЫХ С COVID-19.

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Аннотация
За период с декабря 2019 года, когда в Китае был выявлен первый случай атипичной пневмонии, появились первые данные об особенностях течения инфекции у пациентов с различными заболеваниями. В частности, появились сообщения о большей подверженности инфекции лиц с сердечно-сосудистыми заболеваниями и, в частности, с артериальной гипертензией, и существенно более высоком риске развития неблагоприятных исходов у этой группы пациентов. Мы приводим анализ имеющихся на настоящий момент

публикаций, касающихся коронавирусной инфекции у лиц с артериальной гипертензией. В статье затрагиваются вопросы рисков у больных артериальной гипертензией на фоне коронавирусной инфекции, в том числе связанных с антигипертензивной терапией (включая блокаторы ренин-ангиотензин-альдостероновой системы), и подходы к ведению таких пациентов.

Ключевые слова: коронавирус, COVID-19, SARS-CoV-2, артериальная гипертензия, сердечно-сосудистый риск, блокаторы ренин-ангиотензин-альдостероновой системы, ангиотензинпревращающий фермент 2, цинк

COVID-19 BILAN KASALLANGAN BEMORLARDA ARTERIAL GIPERTONIYANING KECHISHI VA DAVOSI.

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Annotatsiya
2019-yilning dekabr oyidan boshlab, Xitoyda SARS-CoV-2 ning birinchi holati aniqlanganidan beri, turli kasalliklarga chalingan bemorlarda infektsiyaning kechish xususiyatlari haqida birinchi ma'lumotlar paydo bo'ldi. Xususan, yurak-qon tomir kasalliklari va xususan, arterial gipertenziya bilan og'rigan shaxslarda infektsiyaga ko'proq moyillik va bemorlarning ushbu guruhida salbiy oqibatlarning sezilarli darajada yuqori xavfi haqida xabarlar mavjud. Biz arterial gipertenziya bilan og'rigan odamlarda koronavirus infektsiyasiga oid mavjud nashrlarning tahlilini taqdim etamiz. Maqolada arterial gipertenziya bilan og'rigan bemorlarda koronavirus infektsiyasi fonida, shu jumladan antigipertenziv terapiya (shu jumladan renin-angiotenzin-aldosteron tizimi blokatorlari) bilan bog'liq xavflar va bunday bemorlarni davolashga yondashuvlar ko'rib chiqiladi.

Kalit so'zlar: koronavirus, COVID-19, SARS-CoV-2, arterial gipertenziya, renin-angiotensin-aldosteron tizimining blokatorlari, angiotensin aylantiruvchi ferment-2, sink.

The coronavirus pandemic has affected all areas of people's lives, including health, economics, education and psychological aspects. It is predicted that the coronavirus

pandemic will cause a new pandemic of non-communicable diseases, mostly cardiovascular (CVD) [3].

When studying the data presented in open medical sources, it was found that the most common concomitant disease complicating the course of the acute period of COVID-19, especially in elderly patients, is arterial hypertension (AH) [4].

Elevated blood pressure remains the leading cause of death worldwide, accounting for 10.4 million deaths per year [1]. AH is a leading risk factor for the development of CVD (myocardial infarction, stroke, coronary heart disease, chronic heart failure), cerebrovascular (ischemic, hemorrhagic stroke, transient ischemic attack) and renal diseases [5].

RAAS includes humoral factors and enzymes with proteolytic activity, through which intracellular cascades of reactions are triggered, which play a leading role in the regulation of blood pressure. The first proteolytic enzyme involved in these processes is renin, synthesized by the kidneys, with the participation of which liver angiotensinogen is cleaved to inactive angiotensin I (AT I). The transition of AT I to angiotensin II (AT II) is carried out by an angiotensin-converting enzyme (ACE) associated with the cell membrane. AT II is the main effector peptide of the RAAS, which, by binding to specific receptors in organs and tissues, mediates various hemodynamic effects of the RAAS. First of all, it is vasoconstriction, pro-inflammatory and proliferative effects, as well as activation of other pressor hormones - catecholamines, aldosterone, vasopressin. There are 4 types of specific receptors for AT II: angiotensin receptors 1, 2, 3, 4 types (AT1, AT2, AT3, AT4 receptors), of which two are the most studied - AT1 and AT2 receptors, which differ significantly as according to the signal reactions regulated through them, and according to the physiological responses of target cells [2].

There are 2 forms of ACE-2 - membrane-bound and soluble [16]. The membrane-bound form of ACE-2 is functionally active and includes an N-terminal ectodomain, a transmembrane domain, and a cytoplasmic domain. The soluble form of ACE-2 is formed by deamination of the extracellular part of the ACE-2 molecule. The process of deamination occurs with the participation of the ADAM17 protease, which is a transmembrane protein [17, 18]. The presence of two forms of ACE-2 plays an important role in the penetration of the SARS-CoV-2 virus into target cells.

The membrane-bound form of ACE-2 is an essential condition for the penetration of SARS-CoV-2 into the target cell, then an increase in the expression and amount of this form of the enzyme in the membrane can contribute to infection with the SARS-CoV-2 virus and aggravate the course of COVID-19. In this regard, it is logical to assume

that in this category of people, who are more susceptible to severe COVID-19, the concentration of ACE-2 in the cells should be the highest.

The penetration of the SARS-CoV-2 virus into the cells of the lungs and other organs through the binding of the spike protein of the virus to the transmembrane form of ACE-2 has become a real revelation for many medical specialists, especially cardiologists, who are well aware of the involvement of RAAS in the pathogenetic processes of most CVDs. The question arose whether the mechanism of penetration of SARS-CoV-2 into target cells can affect the severity of the disease and mortality, especially in the context of the presence of concomitant hypertension in patients [6].

Viral diseases occur with various symptoms, including changes in the cardiovascular system, namely, destabilization of blood pressure levels. These phenomena can be observed both in healthy individuals and in patients with hypertension. The latter are most susceptible to changes in the blood pressure profile during acute respiratory diseases. The reaction of the CCC, as a rule, is most pronounced against the background of febrile conditions. Fluctuations in blood pressure against the background of an increase in body temperature can be both in the direction of increasing blood pressure, and its significant decrease to a level to which the patient is not adapted. At the peak of fever, an increase in blood pressure is a consequence of spasm of peripheral vessels, and during a critical drop in temperature due to vasodilation, increased diuresis, blood pressure decreases and can lead to hypotension up to collapse. Pronounced uncontrolled fluctuations in blood pressure are associated with a high risk of developing cardiovascular complications (CVC) in patients with hypertension, primarily stroke and acute coronary syndrome [7].

One of the pathogenetic mechanisms of worsening of the course of hypertension in COVID-19 may be due to the involvement of the central nervous system. A significant level of ACE-2 expression was found not only in the lungs, but also in some parts of the brain. A high content of SARS-CoV-2 viral particles was found in the brainstem and cranial nerves extending from it [8].

As a result of viral damage, apoptosis of these cells was noted, which led to disruption of the functioning of the brain centers responsible for the regulation of blood pressure and respiration. In addition, a decrease in the level of ACE-2 in the brainstem can cause a violation of the tone of the sympathetic nervous system and lead to destabilization of blood pressure in patients with hypertension [9].

Five major classes of antihypertensive agents are currently recommended for the treatment of hypertension [5]. First-line drugs are inhibitors of RAAS activity - angiotensin-converting enzyme inhibitors (ACE inhibitors), which block the formation of AT II, and angiotensin receptor blockers (ARBs), which block the

interaction of AT II with its receptors. ACE inhibitors and ARBs, having a pronounced antihypertensive effect, are most often used for the treatment of hypertension with a large evidence base of cardio-, nephro-, cerebroprotection and reduction of cardiovascular complications.

Attempts have been made to study the possible negative impact of RAAS blockers on the course of the disease by using them in patients with COVID-19 and evaluating the effects. Currently, this study is ongoing (Clinical Trials.gov Identifier: NCT04312009), but with a different goal - to evaluate the effectiveness of RAAS blockade in severe COVID-19. An interesting study by K. Kuba et al. showed that infection of mice with both viruses, SARS-CoV and SARS-CoV-2, led to a decrease in ACE-2 expression and was associated with more severe lung damage. The researchers showed a seemingly paradoxical result that ACE-2 protects the lungs of mice from developing ARDS. Severe lung injury could be prevented by the administration of ARBs [10,23].

It has been established that the SARS-CoV-2 coronavirus enters the cells of the human body by binding the S protein located on the surface of the virus to the extracellular domain of the membrane form of angiotensin-converting enzyme type 2 (ACE2), while its affinity exceeds that of the SARS-CoV virus [15, 11]. ACE2 is expressed in cells of the epithelium of the lungs, intestines, kidneys and endothelium, in muscle cells, which determines the nature of the lesion during the infectious process [12,22]. D. Batlle et al. put forward a hypothesis that the circulating form of ACE2, the concentration of which is usually low, can bind in a competitive manner to the S protein of the virus, thereby preventing its entry into the cell [11], which was confirmed in an in vitro experiment and which reveals perspective for the development of therapeutic drugs containing a soluble form of human recombinant ACE2 (APN 01) (Clinicaltrials.gov #NCT04287686) [13, 14].

At the same time, the interaction of long-term prescribed drugs with other factors cannot be excluded. Thus, it has been shown that various antihypertensive drugs (diuretics, calcium channel blockers, ACE inhibitors, beta-blockers) affect the metabolism of electrolytes and microelements [19, 20]. In particular, in patients with newly diagnosed hypertension, monotherapy with diuretics, calcium channel blockers, and ACE inhibitors leads to a change in the concentration of zinc ions (an increase in zincuria and a decrease in the level of zinc in the blood while taking diuretics, a decrease in the content of zinc in the blood serum when taking ACE inhibitors and a decrease in the concentration of zinc in erythrocytes during the use of calcium channel blockers), which can be explained by the suppression of zinc reabsorption by the kidneys and an increase in zincuria [19, 21]. When correcting the

diet with its enrichment with microelements in patients taking antihypertensive drugs, this effect decreases and the content of zinc ions is restored [20].

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