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REVIEW ARTICLE

Relationship between COVID-19 and Arterial Hypertension

Relación entre COVID-19 e Hipertensión Arterial

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ABSTRACT

Introduction: The first three months of 2020 have been influenced by the spreading of a pandemic caused by the SARS-coronavirus 2, which causes COVID-19 infection that in some cases is associated with acute respiratory distress syndrome.

Objective: To identify the relationship between COVID-19 and hypertension.

Material and Methods: A bibliographic review was carried out using database search engines. In addition, reference literature in Cardiology was used as well as information from official government websites such as WHO/PAHO and other scientific societies.

Development: Coronaviruses enter into target cells through a spike S protein, whose S1 surface unit is coupled to the angiotensin-converting enzyme 2 as a receptor. In the different revised series, the clear relationship between the history of arterial hypertension and the unfavorable evolution is observed in patients with COVID-19. In an extensive literature search, there is no scientific evidence for discontinuation of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in hypertensive patients with COVID-19.

Conclusions: The angiotensin-converting enzyme acts as a SARS-CoV2 receptor. Hypertensive individuals have a less favorable evolution course of the condition caused by this virus. Discontinuation of treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is not advisable in hypertensive patients with COVID-19.

Keywords: COVID-19, SARS-CoV 2, 2019-Ncov, SARS, coronavirus, hypertension.

RESUMEN

Introducción: El primer trimestre de 2020 se ha visto influenciado por la propagación de una pandemia ocasionada por el virus SARS coronavirus 2, el cual origina una afección (COVID-19) que en algunos casos llega al Síndrome de Distress Respiratorio Agudo.

Objetivo: Identificar la relación existente entre COVID-19 y la Hipertensión Arterial.

Material y métodos: Se realizó una revisión, utilizando bases de datos bibliográficas y buscadores. Además, se utilizó literatura de consulta obligada en Cardiología e información de sitios web oficiales gubernamentales, de la OMS/OPS y sociedades científicas.

Desarrollo: Los coronavirus se unen a sus células diana a través de una proteína espícula (S), cuya unidad de superficie S1 se acopla a la enzima conversora de angiotensina 2 como receptor. En las diferentes series revisadas se observa la clara relación entre el antecedente de Hipertensión Arterial y el curso evolutivo desfavorable en pacientes con COVID-19. Al realizar una búsqueda extensa de la bibliografía no se encuentra evidencia científica que ampare la suspensión del tratamiento con inhibidores de la enzima conversora de angiotensina/ antagonistas de los receptores de angiotensina en pacientes hipertensos con COVID-19.

Conclusiones: La enzima conversora de angiotensina actúa como receptor del SARS-CoV 2. Los individuos hipertensos presentan un curso evolutivo menos favorable de la afección por este virus. No es aconsejable la suspensión del tratamiento con inhibidores de la enzima conversora de angiotensina o antagonistas del receptor de angiotensina en pacientes hipertensos afectados con COVID-19.

Palabras claves: COVID-19, SARS-CoV 2, 2019-nCOV, SARS, coronavirus, Hipertensión.

INTRODUCTION

The first three months of 2020 have been influenced by the spreading of a pandemic caused by the SARS-coV-2, which causes COVID-19 infection that, in some cases, leads to a severe acute respiratory syndrome (SARS) and a fatal outcome. Cuba does not escape from this global situation.[1,2]

As for writing this article (March 24), WHO had reported a total of 332 930 confirmed cases with 14 510 deaths from this condition. Europe was considered the region most affected by the pandemic with 171 424 confirmed cases.[3]

In the region of the Americas, 40 441 confirmed cases and 504 deaths were reported. The most affected country was the United States with 33 337 cases and 415 deaths.[4]

In Cuba, a total of 40 confirmed cases, 1 036 hospitalized suspicious cases, and 1 death were reported.[5] Because of this situation, the Cuban government adopted a set of measures to face the situation.[6]

In Cuba, heart diseases are the first cause of death with a total of 25 684 deceases in 2018 (incidence rate of 228,2 per 100 000 inhabitants) and 4 404 of these deaths were caused by Systemic Arterial Hypertension (SAH); that is, High Blood Pressure (HBP) which presented a prevalence of 225,2 per 1000 habitants that year.[7] On the basis of this information, it is logical that several researchers such as Naranjo-Dominguez et. al.[8] have shown concern over the issue.

The **objective** of this research is to identify the relationship existing between the COVID-19 and Hypertension.

MATERIAL AND METHODS

A biblographic review was performed between 17 and 23 March, 2020. The search for information was carried out in databases such as *PubMed/ Medline*, *ScienceDirect* and *SciELO*; using Google Scholar as search engine.

For the collection of information, a search strategy was applied using the following key words and connectors: COVID-19 and Hypertension, SARS-CoV-2 and Hypertension, 2019-nCOV and Hypertension, SARS and Hypertension, and coronavirus and Hypertension (relevance filtering).

In addition, reference literature in Cardiology and information from official government websites such as WHO/PAHO and other scientific societies were used.

A total of 33 bibliographical sources of information in Spanish and English were selected to conduct this research.

DEVELOPMENT

On December 12, 2019, a new respiratory infectious disease appeared in Wuhan, province of China.[9] An initial group of cases were related to a seafood market in Huanan as a result of the contact of individuals with the animals that were sold in that market. Later on, it was observed that human-human transmission also occurred, causing a quick spreading of the disease throughout China.[10]

In these patients, a new virus closely related to the SARS-CoV, which was named SARS-CoV-2, was isolated; this new virus was identified as the etiological agent of this new respiratory infection.

According to other research studies, bats were identified as the reservoirs of the progenitor of the virus, although there are reports that explain that it has been isolated in other animals.[11]

Coronaviruses are single-stranded RNA viruses belonging to the family Coronaviridae. This family is divided into two groups: Coronavirinae and Torovirinae. Its name is due to electron microscope observations of the presence of protein projections that have a crown-like appearance.[1]

For a long time, coronaviruses were considered benign pathogens. It was not until 2002 that, in the Guangdong province of China, an outbreak of severe acute respiratory syndrome (SARS) occurred, which subsequently spread to the rest of the world. At that time, there was demonstrated evidence that it was produced by a coronavirus, which was identified as SARS-CoV, and caused atypical pneumonia with a mortality rate of 10 %. Due to the high morbidity and mortality associated with the outbreak of SARS, studies were initiated about this virus family. These studies allowed subsequent identification of a novel coronavirus such as MERS-CoV, which was the causing agent of the Severe Acute Respiratory Syndrome in the Middle East where the natural host is the camel, with subsequent human transmission[1]

The COVID-19 appears after an incubation period of about 5,2 days. The period between the onset of symptoms and the death ranges from 6 to 41 days with an average of 14 days. This period depends on the age of the patient and the status of the immune system.[12]

The most common symptoms of COVID-19 are fever, cough and fatigue; other associated symptoms may be secretions, headache, hemoptysis, diarrhea, shortness of breath, and sore throat; other serious forms such as acute respiratory distress syndrome (ARDS) can also appear.[12]

In January 2020, Wan et al.[13] published a work in which they reported the association between angiotensin converting enzyme (ACE) and the pathophysiology of SARS-CoV-2.

Coronaviruses enter into target cells through a spike S protein, whose S1 surface unit is coupled to the angiotensin-converting enzyme 2 as a receptor. This mechanism, which was described above in the SARS-CoV virus, is the same as the one used by the SARS-CoV-2 virus.[10]

ACE 2 has two forms: a circulating soluble form and another complete form that is predominant in type II pneumocytes. This complete form has a structural transmembrane domain which binds spike S protein of SARS-CoV-2.[14]

According to an editorial published by Fang et al. in *The Lancet,*[15] based on the information previously given, which states that the expression of ACE 2 is increased in patients treated with angiotensin-converting enzyme inhibitors (ACEI) and / or antagonists of angiotensin receptor blockers (ARBs) and that this increased expression provides more potential recipients to the SARS-CoV-2, these authors present the hypothesis that hypertensive patients or other patients suffering from cardiovascular diseases who require treatment with ACEI / ARB have an increased risk of developing severe forms of COVID-19.

Renin is an enzyme that is stored in inactive form renin (prorenin) in the juxtaglomerular cells of the kidney, and when blood pressure falls, a release of renin which acts on a globulin called angiotensinogen occurs, resulting in the production of angiotensin 1 which has light vasoconstrictor properties that are insufficient to significantly alter the circulatory function. ACE enzyme is present in the lungs and, to a lesser extent, in the heart and systemic vasculature which is responsible for the conversion of angiotensin I in the octapeptide with biological activity of angiotensin II to the splitting of two amino acids, in addition to intervening in degradation of bradykinin. Angiotensin II is a potent vasoconstrictor that is modified through two mechanisms of blood pressure. In the first of them, peripheral vascular resistance is increased by the intense vasoconstrictor activity on arterioles; in the second one, the direct salt and water retention in the kidneys or aldosterone secretion by the suprarenal glands, results in long term vascular inflammation and cardiac remodeling.[16,17]

There are 2 main types of angiotensin receptors: the ATI 1 distributed in renal vessels, blood, suprarenal glands, heart, liver and brain that are responsible for most hypertensive effects of angiotensin II and constitute an important therapeutic target in the treatment of hypertension and cardiovascular disease progression. The ATI 2 receptors are found in the fetus, the uterus, ovaries, suprarenal glands which are attributed vasculature and vasodilator effects although they are not well studied in humans.[17]

At present, the *Clinical Practice Guidelines* recommend a combination therapy for most hypertensive patients based on scientific evidence gathered from numerous clinical trials and meta-analyses. There is a general consensus among societies of cardiology on the absolute benefit of ACEI drugs and / or ARBs drugs in the decrease of blood pressure levels and the reduction in greater cardiovascular and cerebrovascular events at a long term either in combination with a blocker calcium channel or a diuretic and in the treatment of heart failure.[18,19,20,21]

An example of this is the ACCOMPLISH trial which evaluated the combination of ACEI and calcium channel blockers in hypertensive patients with risk factors obtaining a 21 % decrease of total cardiovascular risk.[22]

LIFE 2002 study evaluated the combination of an ARB and a diuretic compared with a beta-blocker and a diuretic in hypertensive patients with left

ventricular hypertrophy, which showed a reduction of 26 % of risk of stroke.[23]

Given the aforementioned facts, it is clearly demonstrated that ACEI and ARBs offer significant benefit to all hypertensive patients which calls into question any non-significant risk that could result.

Although the pathophysiological theory underlying the relationship between ACE 2 and SARS-CoV-2; to date, there are no studies correlating statistically significant consumption of ACEI or ARBs with an unfavorable clinical course of COVID-19. However, the association between HBP as underlying disease and complications in patients with COVID-19 has been demonstrated, as discussed below. It is valid to explain that not all hypertensive patients take ACEI or ARBs, since there are other first-line antihypertensive drugs. Therefore, this association may respond to other causes or covariates, but not necessarily to the aforementioned theory.

In a retrospective cohort study conducted by Zhou et al.[24] with 191 individuals with COVID-19 in Wuhan, China, HBP was statistically significantly associated with fatal outcome (OR 3,05, 95 % CI 1,57 to 5,92; p = 0,001), but this result was not repeated in the multivariate analysis, which could be influenced by other covariates.

Another Chinese study conducted in 1 099 patients showed that 23,7 % of individuals who presented severe forms of the disease had history of HBP, while HBP was present in 13,4 % of those who did not develop severe disease. The mean age was also higher in the subgroup with unfavorable evolution (52 vs. 45) as well as the antecedent of diabetes mellitus (DM) (16,2 % vs. 5,7 %) and ischemic heart disease (5,8 % vs. 1,8 %).[25]

A recent meta-analysis carried out with 19 and 656 individuals showed that the HBP (present in 18,6 % individuals) was significantly associated with COVID-19 (p <0,001). The presence of other cardiovascular diseases (14,6 %; p <0,001) and age (mean 51,97 years, p <0,001) also yielded association analysis.[26]

A bibliographic review conducted by Lai et al.[27] concluded that the unfavorable evolution of patients with COVID-19 is more likely in the elderly or those with comorbidities such as HBP, other cardiovascular diseases, and Diabetes Mellitus.

A research conducted in Wuhan, China, the initial epicenter of the pandemic, which studied 140 individuals with COVID-19, showed a higher prevalence of HBP in patients who developed severe forms with regard to those with a better progression, but this does not lead to a statistical significance unlike other variables such as age (64 vs. 51, p <0,01).[28] This result calls into question whether the relationship between history of HBP and the unfavorable evolution in the course of the COVID-19 can be due to the increased prevalence of cardiovascular disease in older adults.

A study published in JAMA, which included 201 people affected by COVID-19, showed a statistically significant association between HBP and the development of ARDS (HR 1,82; 95 % CI: 1,13 to 2,95; p = 0,01). Other variables such as age

and DM showed a statistically significant association with this complication.[29]

Yang et al., performed a meta-analysis that included 46 248 patients, which showed that HBP is associated with severe forms of COVID-19 (OR 2,36; 95 % CI: 1,46 to 3,83). History of other cardiovascular diseases or chronic respiratory diseases showed a similar association analysis.[30]

The table presented below shows the percentage of hypertensive patients in the different series of COVID-19 reviewed, based on its evolution. This clear relationship between this cardiovascular antecedent and the unfavorable evolution in patients with COVID-19 is observed, although in some cases, this relationship is not so clear or could, according to the authors of this article, be influenced by other covariates as the presence of other basic cardiovascular conditions, smoking habit, DM and age, which are known to be involved in both pathologies.

Table - Percentage of hypertensive patients in the different series of COVID-19 based on its evolution [24,25,26,28,29,30]

Article	Population	Total hypertensive patients		Mild forms/ survivors		Severe forms/ deceased	
		No.	%	No.	%	No.	%
Zhou, *et al.*[24]	191	58	30,0	32	23,0	26	48,0
Guan, *et al.*[25]	1099	165	15,0	124	13,4	41	23,7
Rodríguez- Morales, *et al.*[26]*	656	___	18,6	Statistically significant association in the meta-analysis			
Zhang, *et al.*[28]	140	43	30,0	20	24,4	22	37,9
Wu, *et al.*[29]	201	39	19,4	16	13,7	23	27,4
Yang, *et al.*[30]*	46 248	___	17±7	Statistically significant association in the meta-analysis			

*Meta-analysis

Despite the aforementioned facts, no scientific evidence that supports the discontinuation of treatment with ACEI / ARB in hypertensive patients with COVID-19 was obtained from the extensive search conducted. Given the potential benefits offered by these drugs and regardless of the cost that brings about the high consumption of ACEI,[31] the authors of this article, in accordance with the information provided by experts of the European Society of Cardiology and the American Association of the Heart, recommend to continue treatment with these drugs until new studies on the topic come to light.[32,33]

CONCLUSIONS

Angiotensin converting enzyme acts as receptor for SARS-CoV-2 promoting their entry into their target cells. Hypertensive individuals have a more unfavorable clinical course of the disease caused by this virus. It is not advisable to discontinue treatment with angiotensin-converting enzyme inhibitors or antagonists of angiotensin receptor blockers in patients with COVID-19 and history of Hypertension due to the cardiovascular benefits they provide and the lack of evidence to demonstrate the association between these drugs and an unfavorable evolution.

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Conflict of interests

All authors declare no competing interests.

Contribution of authorship

AGH: bibliographic search for renin-angiotensin – aldosterone system in cardiovascular disease and COVID-19
JMRV: bibliographic search for the relationship between Hypertension and COVID- 19, COVID-19 epidemiology
JLE: bibliographic search for historical background, clinical and microbiological aspects of the infection by SARS-CoV-2
All authors participated in the bibliographic search, the scientific writing, and all of them have approved the final version of the text.