Review Article

Antihypertensives and COVID-19: A Narrative Review

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Abstract

Coronavirus disease 2019 (COVID-19): A plague which has impacted health and economy worldwide on an exceptional scale. Patients have diverse clinical outcomes, but those with preexisting cardiovascular disease, hypertension, and related conditions sustain strangely worse outcome. Hypertension is a significant risk factor of mortality worldwide and it has been focused more nowadays because of its association with novel coronavirus 2 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection mentioned as COVID-19. Patients showing severe COVID-19 infections mostly seen to be older and had a history of hypertension. Most of the patients who have died within the pandemic were known cases of hypertension. This article demonstrates the relation between angiotensin-converting enzyme 2 (ACE2) and COVID-19 with its possible mechanisms. Hence, with this review, we have raised multiple questions regarding a more severe course of COVID-19 in regard to hypertension itself and thus the antihypertensives used. With the data available, it is quite clear that the infection is understood to be caused by the SARS-CoV-2 and is responsible for human-to-human transmission of disease, entering the cells through its predicated receptor ACE2.

Keywords: Angiotensin-converting enzyme inhibitors, antihypertensives, COVID-19, hypertension

Introduction

The coronavirus infection coronavirus disease 2019 (COVID-19) first presented as an epidemic of atypical pneumonia in Wuhan, China, on December 12, 2019.[1,2] Since then, it is spread globally to infect and kill many people in over 200 countries till date. COVID-19 has affected not only the health but also the economy also on an unprecedented scale.

Whereas COVID-19 is essentially a respiratory tract infection, it is important systemic effects including on cardiovascular (CV) and immune systems. Patients with preexisting CV conditions represent large proportions of patients with symptomatic infection, and knowledge suspiciously worse outcomes at between 5 and 10-fold increase in mortality (World Health Organization).[3]

Novel coronavirus 2019 disease (COVID-19) has been widely reported extensively in patients of hypertension with an increased severity and mortality. The report of an apparently high prevalence of systemic arterial hypertension in severe COVID-19 cases in an initial Chinese report on the one hand[4] and therefore the concept that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may use angiotensin-converting enzyme 2 (ACE2) – an enzyme potentially upregulated by blockers of the renin–angiotensin system[5] – as a viral entry receptor in lung cells on the opposite hand[2,6] has raised concerns.

This infection showing a human-to-human transmission of disease is understood to be caused by the SARS-CoV-2[7] and theoretically known to enter the cells through its predicated receptor ACE2.[8] The function of this enzyme is to catalyze the conversion of angiotensin II to angiotensin 1–7, a peptide which opposes the pro-inflammatory, pro-oxidative, vasoconstrictive, and fibrotic properties of angiotensin II.[9] This association between SARS-CoV-2 and ACE2 suggested that hypertension could act by two ways in the pathogenesis of COVID-19,

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either by playing an immediate role as a preexisting clinical predictor of disease severity, or by imparting to deterioration late in disease course, characterized by acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, and/or multiple organ failure.[10]

The clinical and epidemiological features of COVID-19 are continually published within the previous couple of weeks. Interestingly, specific comorbidities connected with increased risk of infection and worse outcomes with the development of increased severity of lung injury and mortality are reported. Hypertension (30%), diabetes (19%), and coronary heart condition (8%) were seen to be the foremost common comorbidities as per one report.[11] Whereas an another report showed that the foremost frequent comorbidities in patients with COVID-19 who developed the ARDS were hypertension (27%), diabetes (19%), and heart disorder (6%).[12]

It's yet like two peas in a pod whether uncontrolled vital sign may be a risk factor for acquiring COVID-19 or whether controlled vital sign among patients with hypertension is or is not less of a risk factor. However, it is quite obvious to maintain the vital signs under control to scale back disease burden, although it is no effect on susceptibility to the SARS-CoV-2 virus infection.[13]

Antihypertensive Drugs and Risk of Coronavirus Disease 2019?

Due to a possible increased risk of worse clinical outcomes in patients with COVID-19, Fang *et al*.[10] recommended that clinicians should think about withholding angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and calcium channel blockers should be advocated in an exchange. . Table 1 shows the hypothesis behind this proposal is that the entry point for SARS-CoV-2 is that the ACE2 receptor which ACEIs and ARBs have the potential to upregulate ACE2. However, this data is largely available from animal studies of heart tissue. Human data have not consistently shown amplified ACE2 levels.[14,19] However, preclinical models of SARS-CoV infection does not support this hypothesis.

In 2005, Kuba *et al*.[15] found that mice after acid aspiration-induced acute lung injury had significantly diminished lung injury and pulmonary edema when treated with losartan compared to mice treated with placebo. Furthermore, severe lung injury and pulmonary edema in ACE2-knockout mice both seen to be prevented in recombinant human ACE2 infusionsor losartan.[16] Administration of recombinant human ACE2 improved lung injury in patients with SARS-CoV infection and in acid aspiration and sepsis-induced models of ARDS.[15,16] Hence, there is a need of an initiation of randomized controlled trials assessing recombinant human ACE2 infusions and losartan specifically in patients of COVID-19. In some other viral pneumonia such as (e.g., H5N1 and H7N9 influenza) also severe ARDS due to impaired ACE2 activity has been identified.[17] When the mice were treated with H5N1 influenza with losartan versus placebo has shown reduced pulmonary edema, pulmonary neutrophil infiltration, and significantly improved survival.[17]

There has been seen an increased ACE2 level on intestine luminal cells in the humans given ACEIs, ARBs, or both, in addition to animal models.[20] Hence, as per the available information, it should be noted that glycosylation modification is important for binding of SARSCoV-2 spike protein. Inhibition of ACE2 glycosylation by either chloroquine, hydroxychloroquine, or a serine Potential Inhibitors (PI) significantly reduces the infection of host cells by SARS-CoV and SARS-CoV-2 *in vitro*[6,21,22] which should be explored thoroughly.

From the info which has been available to us suggests that ACE2 may be a double-edged sword, particularly when considering patients with SARS-CoV-2 infection and comorbidities of hypertension, diabetes, and heart disorder.

Theoretically, spironolactone has been known to hamper ACE-2 expression on lung-cell surfaces, because unlike ACEIs/ARBs, it does not act within the pulmonary renin–angiotensin–

Table 1: Studies on antihypertensives and angiotensin-converting enzyme 2

Author and year	Studied on	Result
Ramchand *et al.* (2018)[19] and Walters *et al.* (2017)[14]	Heart tissue of animals, no human data available	Based on the hypothesis that ACEIs and ARBs have the potential to upregulate ACE2. Hence, ACE2 being the entry point for SARS-CoV-2
Kuba *et al.* (2005)[15]	Mice treated with losartan and other group included placebo	Significantly diminished lung injury and pulmonary edema when compared with mice treated with placebo
Imai Y, Kuba K, Rao S, *et al.* (2005)[16]	ACE2-knockout mice when treated with recombinant human ACE2 infusions or losartan	Both of them were seen to be preventing severe lung injury and pulmonary edema
Vuille-dit-Bille RN, Camargo SM, Emmenegger L, *et al.*, (2015)[20]	ACEIs, ARBs, or both given to the humans	Showed increased ACE2 levels on intestine luminal cells
Sawathiparnich *et al.* (2002)[24]	Spironolactone	Cut down ACE-2 expression on lung-cell surfaces which can prevent complications

ACE2: Angiotensin-converting enzyme 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, ACEIs: ACE inhibitors, ARB: Angiotensin receptor blockers

aldosterone system (RAAS). Although renin levels are superior when using ACEIs, ARBs, or potassium-sparing diuretics, the difference between the sites of blockade of renin effects may cause a contrary metabolic microenvironment within the RAAS in the lungs.[18,23,24]

The benefits of spironolactone are extensively validated for safety/risk profile, and its ability to replace for ACEIs/ARBs appropriately would allow this switch without major ethical concerns in selected patients. ACEIs/ARBs might be a risk factor due to elevated ACE-2 activity in plasma and cell surfaces. The use of spironolactone may tackle the problems of withdrawal of ACEIs/ARBs and simultaneously rebalance plasma and cell-membrane levels of ACE-2.

Despite the lack of evidence, there have been advocates for both the use and cessation of ACEIs, ARBs, or both during the treatment for COVID-19 in patients with hypertension.[25] A systematic review and metaanalysis conducted on ACEI/ARB use and risk of infection or severity or mortality of COVID-19 stated that current evidence did not confirm the concern that ACEI/ARB exposure is harmful in patients with COVID-19 infection. Hence, the study was in favor of the current guidelines that deject discontinuation of ACEIs or ARBs in COVID-19 patients and the setting of the COVID-19 pandemic.[26] In a population-based case–control study, a total of 6272 case patients with SARS-CoV-2 were assessed as per sex, age, and municipality of residence at Italy. Results revealed that the use of ACE inhibitors and ARBs was more frequent among patients with COVID-19 than among controls because of their higher prevalence of CV disease. Nonetheless, there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.[27]

Conclusion

With the data available, it is quite clear that the infection is understood to be caused by the SARS-CoV-2 and is responsible for human-to-human transmission of disease, entering the cells through its predicated receptor ACE2. However, this data still is not in favor of abruptly stopping/changing the antihypertensives. More studies especially within the sort of randomized controlled trials are going to be needed to prove the association of ACEIs/ARBs and COVID-19 also as other antihypertensives. Since without proper knowledge, stopping/replacing the drug will ultimately increase the health-care burden only which is not in the least feasible during this period of crisis.

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Conflicts of interest

There are no conflicts of interest.

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