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Hypertension in the Era of COVID-19 Pandemic: a Mini Review

Dimitrios Chatzis[1]*, Zeyad Al-Jazrawi[1], Ismini Tzanaki[1], Nikos Karpettas[1], Ioannis Pantazopoulos[1,2] and Ioannis Patrikios[1]

[1]Medical School, European University Cyprus, Greece

[2]Department of Emergency Medicine, University of Thessaly, Greece

Abstract

SARS-Cov-2 infection is the causal agent of coronavirus disease 2019 (COVID-19) which has been characterized as a pandemic by the World Health Organization (WHO). This disease has killed over 300,000 people worldwide as of May 15th, 2020 and it seems that underlying cardiovascular disease represents important comorbidity associated with clinical deterioration and adverse outcomes in COVID-19 individuals. Initial reports claimed that hypertension may be associated with increased risk of SARS-Cov-2 infection but it seems now that this relationship is rather confounded by older age and hypertension-related comorbidities. Moreover, despite the initial hypotheses linking RAAS blockers use with greater risk of SARS-Cov-2 infection and a more severe COVID-19 course, it is now known that there are no sound scientific data in humans in support of these. Major international scientific organizations unanimously recommend the continuation of RAAS blockers treatment in patients with compelling indications.

Keywords: SARS-Cov-2; COVID-19; Hypertension; Treatment; RAAS blockers

Correspondence to: Dimitrios Chatzis, Medical School, European University Cyprus, Singrou 76 avenue, 11742, Athens, Greece; E-mail: dimitrioschatzis@yahoo.com

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Introduction

On December 31st, 2019, several cases of pneumonia of unknown etiology in Wuhan, Hubei province, China were reported to the World Health Organization (WHO) [1] and they were linked to Huan Seafood Wholesale Market [2,3]. The virus that was responsible for the outbreak of pneumonia was a coronavirus named Severe Acute Respiratory Syndrome- coronavirus-2 (SARS-CoV-2) [4,5] and COVID-19 (coronavirus disease 2019) was the name given to the associated disease which has been officially acknowledged by the WHO as a global pandemic on March 11th, 2020 [6]. COVID-19, as of June 14th, 2020, has affected a total of 7,940,469 people-almost one-fourth of whom reside in the USA and killed almost 433,932 individuals worldwide. Although 4,079,610 have recovered so far, global healthcare systems are still burdened with 3,426,927 active cases, of whom 54,133 are in serious life-threatening condition and a great proportion of them suffer from certain comorbidities, such as hypertension, diabetes mellitus, or cardiovascular diseases [7].

Regarding viral transmission, it is known that SARS-CoV-2 is present in respiratory droplets [8], while the airborne spread of the virus is not established yet [9,10]. Additionally, SARS-CoV-2 has been identified in some bodily fluids, including blood, saliva, cerebrospinal fluid, urine, and tears; however, it is not known yet whether it can be transmitted via these biological materials [6,11]. Spread of SARS-CoV-2 through the fecal-oral route is considered feasible, however, this has not been confirmed yet [12,13].

Patients infected by SARS-CoV-2 can present with non-specific symptoms, and some can even be asymptomatic, at the time they test positive [14]. Usually the incubation period varies between 1 to 14 days, but affected individuals frequently present with symptoms around the 5th-day post-infection [15,16]. The cardinal clinical manifestations of COVID-19 simulate that of viral pneumonia. Mild cases are characterized by the presence of non-specific symptoms such as fatigue, fever, malaise, headache, dry or productive cough, sore throat, anorexia, and shortness of breath. In some instances, the gastrointestinal tract can be affected as well [6]. Regarding the severe cases of COVID-19, they usually manifest as severe pneumonia and sometimes they are accompanied by lethal complications, such as acute respiratory distress syndrome, septic shock, or acute kidney injury, leading to renal failure [14]. Notably, almost 80% of patients have mild symptoms, whereas approximately 14% have a severe form of the disease and nearly 5% are considered to be critically ill [17]. The elder demographic is more susceptible to infection compared to younger ones and the severe form of the illness mostly occurs in the elderly [17,18]. Moreover, it needs to be emphasized that older patients with comorbidities, as well as, immune compromised subjects, are at increased risk of deterioration even if their initial clinical presentation is mild. These specific patients may also often present with atypical clinical features, thus further perplexing timely diagnosis of COVID-19 [19].

Main characteristics of SARS-CoV-2 virus

SARS-CoV-2 is a member of the Coronaviridae family [6]. It

is a positive-sense, single-stranded RNA virus with a size of 29,891 nucleotides, encoding for 9860 amino acids [20]. Studies have demonstrated that SARS-CoV-2 can exist in 2 different forms, denoted as L and S strains [21].

Structurally, SARS-CoV-2 consists of:

- Nucleocapsid protein.
- Membrane protein, found extensively on the surface of SARS-CoV-2, being responsible for viral aggregation [22].
- Spike glycoproteins, promoting viral attachment to human cells that bear ACE2 receptors [23].
- Envelop protein, further aiding in viral aggregation, and increasing the membrane penetrance of human cells [24].

Different non-structural proteins have been identified as well [22]. Even though the exact mechanism of action of SARS-CoV-2 is still unknown, several pathophysiologic mechanisms have been proposed and they all take advantage of the structural characteristics of the spike glycoprotein receptor binding domain of SARS-CoV-2, that is believed to be responsible for the greater binding capacity of SARS-CoV-2 for Angiotensin converting enzyme 2 ACE2 [25]. The spike glycoproteins of SARS-CoV-2 bear a furin - like cleavage site not found in other coronaviruses, conferring unique pathophysiological characteristics to SARS-CoV-2 [26]. SARS-CoV-2 enters human cells via endocytosis. Specifically, the spike glycoproteins of SARS-CoV-2 bind to the ACE2 receptors on human cells and then a cascade of events that promote viral entry is initiated [27-29]. ACE2, is an enzyme detected on the outer surface of cells and it is mainly found in the lungs, but also in other tissues, such as vessels, heart, gastrointestinal tract or kidneys. The binding of SARS-CoV-2 to ACE2 in the lungs is facilitated by the transmembrane protein serine 2 (TMPRSS2) [30]. (Figure 1) summarizes the main pathophysiologic mechanisms and clinical manifestations of SARS-CoV 2 infection.

Structural Protein	Function
Nucleocapsid protein	It is attached to the viral RNA and it promotes viral replication and transcription.
Membrane protein	It is found on the surface of SARS-CoV-2 and promotes viral aggregation.
Spike glycoproteins	Promote viral attachment to human cells that have ACE2 receptors.
Envelop protein	Increases membrane penetrance of human cells and participates in viral aggregation.
Non – structural proteins	The processes of replication and transcription that occur in the cytoplasm, involve the presence of the replication/transcription complex that consists of non-structural proteins [31].

It is well established that patients over the age of 65 are at increased risk of lower respiratory tract infections such as community-acquired pneumonia (CAP), as well as of associated severe complications and a higher mortality rate [32,33]. In this specific age group, hypertension is commonly reported as a co-morbidity. A Spanish population-based study reported that an increased incidence of CAP is linked with increased age but not with hypertension [33]. Furthermore, a similar Finnish study also recognized hypertension as the most common comorbidity (36.4%) in patients aged 65 and older suffering from pneumonia [34]. Importantly, the same study revealed that older age, lifestyle factors, and other comorbidities such as diabetes, but not hypertension, were independently associated with the risk of pneumonia [34]. However, there seems to be an increased risk of cardiovascular events in individuals suffering from CAP or lower respiratory tract infections in general [35].

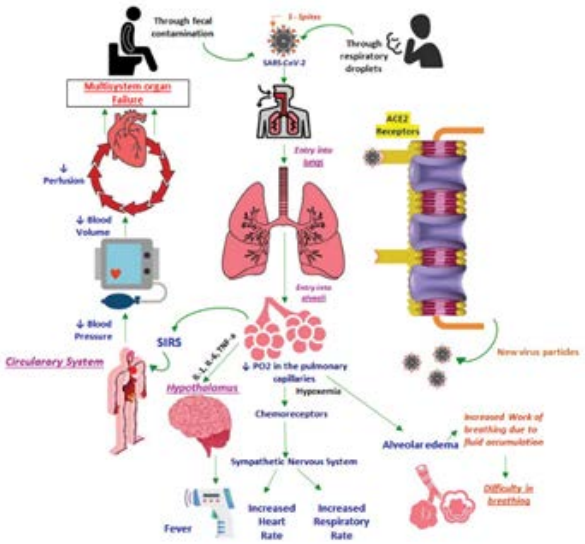

Figure 1: Main pathophysiologic mechanisms and clinical manifestations of SARS-CoV 2 infection. Angiotensin Converting Enzyme 2 (ACE2), Systemic Inflammatory Response Syndrome (SIRS).

The increased risk of hypertensive patients being affected by COVID-19 and their worse prognosis throughout the disease is still a debatable issue. The increased prevalence of pre-existing hypertension in COVID-19 patients who developed the severe disease and the initial Chinese reports that identified hypertension as one of the most common comorbidities (20-30%) in COVID-19 patients requiring ventilation due to severe respiratory complications of the disease [36] have been the initial triggers for this debate. In another Chinese study involving 20,982 COVID-19 patients it was found that 12.26% were self-reported hypertensives and 39.7% of the 406 deceased subjects were also hypertensives; however, it is important to note that 81% of those were over 60 years old [17] and that 23.2% of the total Chinese population over 18 years of age are hypertensives [37]. Further to the aforementioned, a single-center observational study in Hubei province, China involving 1178 patients, revealed that hypertensive patients generally had more severe and even fatal course of the disease [38]. Also, an observational study in Italy showed that 73% of deceased COVID-19 patients were hypertensive. However, it is crucial to note that Italy's high case fatality rate is likely attributed to the older population [39] the median age of fatal cases reported in the study was 79 years [40].

It seems that the frequent coexistence of hypertension in COVID-19 patients [36] is rather a matter of older age, as elderly individuals are more susceptible to COVID-19 [41], and also it is well known that approximately 50% of people over the age of 60 are hypertensive [36]. This, therefore, limits the implication of a causal relationship between hypertension and COVID-19. Moreover, hypertension may be a proxy for the presence of other underlying cardiovascular risk factors such as diabetes, all of which have a higher prevalence of increased age. Thus, the generalization and association of hypertension and COVID-19 are likely to be confounded by age and other co-morbidities [36]. In any case, hypertension management and blood pressure control are of paramount importance to decrease cardiovascular risk [41].

A theoretically valid mechanistic link between hypertension and COVID-19 could be related to the newly reported immune dysregulation phenomenon seen in hypertension [42]. The rapid deterioration in the clinical course of COVID-19 patients has been associated with the

so-called pro-inflammatory "cytokine storm" implying the increased release of certain molecules, such as Interleukin-2,6,7 (IL-2,6,7) and tumor necrosis factor-A (TNF-A) amongst others [10]. Interestingly; clinical [42], experimental, and interventional studies have reported the same cytokines to be key factors even in the course of hypertensive disease. Furthermore, IL-6 which is reported to have a strong association with the clinical outcome of COVID-19 patients [43], also appears to be a key cytokine in the immune-inflammatory response seen in hypertension [35]. Moreover, loss of lymphocytes which represents a hallmark feature of COVID-19 pathophysiology may also have a causal relationship with hypertension [44]. Last, but not least, hypertension may also contribute to the COVID-19 associated "cytokine storm" as $CD4^+$ and $CD8^+$ are both decreased in hypertensive subjects [35].

The aforementioned mechanisms may explain the increased likelihood of hypertension-induced end-organ damage, providing thus the rationale for the association of hypertension with severe COVID-19. To date though, there is not enough data to make firm conclusions, and large-scale observational studies with adjustment of appropriate variables such as age are needed to further clarify the whole concept [35] (Figure 2).

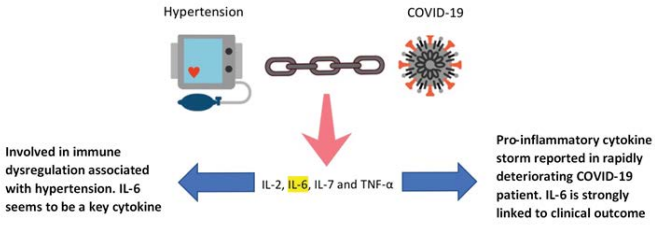

Figure 2: Possible explanation regarding the link between Hypertension and COVID-19.

The use of RAAS blockers in the COVID-19 era

An even more controversial topic is the effect of the Renin-Angiotensin-Aldosterone system (RAAS) - Blockers - the backbone of therapy for hypertension [45] on the risk, severity, progression, and outcome of COVID-19. This has come into light due to the hypothetical connection between COVID-19 and the RAAS via a common link; ACE2. It has been shown that SARS-CoV-2 utilizes its' spike protein to gain entry into its target cells by binding to ACE2 [35] which is found in abundance in the lungs, kidneys, brain, and GI tract.

The RAAS is also a major factor in cardiac and renal function and plays a crucial role in blood pressure regulation. The principle effector of RAAS is angiotensin-2 (ANG2) which acts on Angiotensin receptor 1 (AT1) and Angiotensin receptor 2 (AT2) receptors to produce vascular effects and aldosterone secretion [35]. ANG2 is produced by the cleavage of ANG1 by ACE and is regulated via negative feedback by ACE2, ANG1-7, and MAS receptors. ACE2 is homologous to ACE but is not affected by ACE-inhibitors [35]. Its' main function is to produce ANG1-7 by the degradation of ANG2 [41], and to a lesser extent cleaves ANG1 to produce ANG1-9 which are then converted to ANG1-7 by ACE leading to an even further decrease of ANG2 levels [35]. ACE2, therefore, brings about vasodilator effects by a decrease in ANG2 and an increase in ANG1-7, as well as protective effects on organs such as the kidney, heart, and others using ANG1-7 binding to MAS receptors [35]. Notably, it has been shown in acute lung injury animal models that the ANG2-AT1R axis leads to a more severe injury and that this can be countered by ACE2/ANG1-7/MASR complex [46]. Increased vascular permeability is a key feature in the pathogenesis of acute respiratory distress syndrome and it has been reported to be explicitly pronounced in ACE2 deficient mice [47]. The decrease in pulmonary ACE2 leads to an increase in DABK/Bradykinin B1R which ultimately leads to a more severe acute lung injury in mice models [35], moreover; experimental studies showing the benefits of ACE inhibitors (ACEI) / angiotensin II receptor blockers (ARB)/ACE2 supplementation, supports that a decrease in ACE2 and an increase in ANG2-AT1R leads to more pronounced and severe lung disease [35]. It is of great importance to note that the decrease of ACE2 in SARS-COV-2 has not been confirmed yet, this hypothesis is simply an extrapolation by the acute lung injury models, also it must be noted that ACE2 levels are not significantly associated with age [35].

ACEI/ARBS have been reported to increase ACE2 expression in animal studies [48,49]. Therefore, it has been hypothesized that their administration could be facilitating infection by potentially increasing SARS-CoV-2 binding to the lung ACE2, and thus increasing the risk of developing severe and potentially fatal COVID-19. However; it has been shown that decreased ACE2 levels lead to pulmonary edema and a consequent decline in lung function which could be reversed by the administration of recombinant ACE2 or losartan [50]. Furthermore, ACE2 down-regulation following SARS leads to an increase in RAAS activity and an increase in pneumonia progression [50]. ACEI and ARB treatment have shown a differential impact on RAAS either directly or indirectly by feedback cycles. It has been shown that ACE2 is consistently unregulated by ARBs however its' modulation by ACEI is shown to be variable [35]. Studies show an increase in urinary ACE2 in hypertensive patients with more than 1-year use of ARB [51], similar findings were found in patients with diabetic nephropathy on ARB for more than 24 weeks [52], however, a different study showed no significant effect in diabetic patients [53]. Therefore, data regarding the actual effect of RAAS-blockers on ACE2 levels are rather scarce and to date, there are no persuasive indications about RAS-blockers administration - induced increase in ACE2 levels, especially in humans [35] (Figure 3).

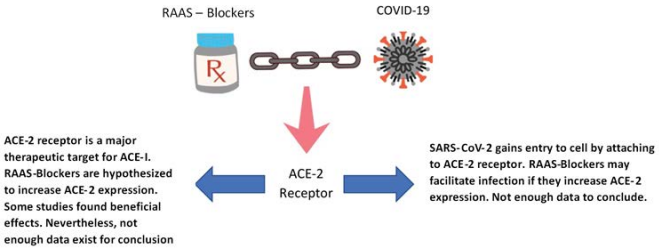

Figure 3: Hypothetical link between RAAS-Blockers and COVID-19. Renin Angiotensin Aldosterone System – Blockers (RAAS-Blockers).

In a retrospective study involving 9 Hubei hospitals and 1128 patients (median age 64 years) with hypertension and COVID-19, 188 of them were taking ACEI/ARB and 940 were on non-RAAS-blockers antihypertensive medications. The unadjusted mortality rate in the ACE/ARB treated subgroup was lower (3.7%) compared to non-ACEI/ARB treated subjects (9.8%). In a mixed effect cox model adjusted for gender, age, co-morbidities, and in-hospital medication, the risk for all-cause mortality was reported to be lower in ACEI/ARB subgroup. Compared to other antihypertensive drugs, ACEI was shown to lower mortality [54]. In another single-center retrospective study, 1178 patients were evaluated, 362 of whom were hypertensive with a median age of 66 years. Patients on ACEI/ARB therapy as compared to their non-RAAS-blockers treated counterparts, did not show a statistically significant difference concerning severe disease and mortality rates [36].

Table 1: The official statement of ACC/AHA/HFSA, ESC and CCS regarding continuation of treatment with RAAS-blockers in hypertensive and heart failure patients diagnosed with COVID-19.

Society	Official statement	Comments
ACC/AHA/HFSA - American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America	"The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently treated with these agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease"	Currently there are no experimental or clinical data demonstrating beneficial or adverse outcomes with background use of ACE inhibitors, ARBs or other RAAS antagonists in COVID-19.
ESC - Council on Hypertension of the European Society of Cardiology	"The Council on Hypertension strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection." Indeed, there is evidence from studies in animals suggesting that these medications might be rather protective against serious lung complications in patients with COVID-19 infection, but to date there is no data in humans.	The speculation about the safety of ACE-i or ARB treatment in relation to COVID-19 does not have a sound scientific basis or evidence to support it.
CCS - Canadian Cardiovascular Society	"The Canadian Cardiovascular Society and the Canadian Heart Failure Society strongly discourage the discontinuation of guideline directed medical therapy (GDMT) involving Angiotensin Converting Enzyme Inhibitors (ACEi), Angiotensin Receptor Blockers (ARB) or Angiotensin Receptor Neprilysin Inhibitors (ARNi) in hypertensive or heart failure patients as a result of the COVID-19 pandemic"	Cessation of these drugs in stable patients can lead to uncontrolled hypertension and increased hospitalizations for heart failure with an unnecessary increase in health care utilization, straining our valuable inpatient hospital resources. There is NO clinical evidence at this time to support withdrawal of these agents.

Covid-19 and hypertension: what is the evidence

Furthermore, in a very recently published population-based study 6272 COVID-19 hypertensive patients residing in the Lombardy region - the epicentre of the epidemic in Italy, were matched to 30759 controls by sex, age, and municipality. The mean age of the patients was 68+/-13 years, 37% of whom being females. It was found that ACEI and ARB use was more common in the COVID-19 subgroup vs. control subgroup; ARB was found to be used in 22.4% of COVID-19 cases vs. 19.2% in controls and ACEI in 23.4% of COVID-19 subject's vs. 21.4% in controls. According to the authors, the use of ACEI/ARB was more frequent in COVID-19 patients, likely due to the increased prevalence of the cardiovascular disease among them. Based on the results of this study, RAAS-blockers use does not seem to increase susceptibility to COVID-19 or the risk of disease progression. This study also suggested an association between loop diuretics and COVID-19 after multivariable adjustment analysis but the authors clarified that this should be regarded as an indicator of the patients' clinical status and underlying diseases such as heart failure and not as a causative association. Those findings are also interesting because the recommended therapy for the majority of hypertensive patients is a combination of either of the RAAS-blockers plus calcium channel blockers (CCB) or thiazides/thiazides-like diuretic [45,55].

Official position of International Scientific Organizations

In accordance with the latest evidence, for the time being, RAAS blockers appear rather reasonable than harmful in the current COVID-19 era. Actually, the withdrawal of RAAS blockers in patients already receiving them will most probably result in an increased rate of cardiovascular complications and mortality [38]. The American College of Cardiology/American Heart Association/Heart Failure Society of America, the Council on Hypertension of the European Society of Cardiology and the Canadian Cardiovascular Society all published their official position-statements regarding the concerns of the use of ACEi/ ARB medications for heart failure and/or hypertension in COVID-19 patients. According to their published reports, they all agree that due to lack of evidence, continuation of the guideline directed medical therapy is strongly recommended [56-58]. (Table 1).

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