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INTERRELATION OF COVID-19 AND HYPERTENSION; A REVIEW STUDY

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Abstract:

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory tract virus that causes Coronavirus disease (COVID-19). The virus originated in Wuhan, China, in December 2019 and has spread to the world. Most patients reported having at least one comorbidities with COVID-19 upon hospital admission. Hypertension, diabetes, chronic obstructive pulmonary disease, obesity, and cardiovascular diseases are among the most commonly reported. Comorbidities are contributing to acute disease prognosis and increased risk of severe symptoms. This review intends to understand how hypertension affect the disease's prognosis and how severe the outcome can be expected

Keywords: SARS-CoV-2, Hypertension, RAAS inhibitors, ARBs

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious and infectious disease caused by the novel coronavirus, severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) [1-2].

In the last two decades, three zoonotic coronaviruses originating from bats have emerged and caused severe respiratory disease in humans: severe acute respiratory syndrome coronavirus(SARS-CoV) Middle East respiratory syndrome coronavirus (MERS-CoV), and, most recently, the pandemic coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. SARS is a zoonosis caused by SARS-CoV, first emerged in China in 2002 and then spread to 29 countries with 8,098 cases with fatality rate of 9.6% [4]. MERS-CoV was the pathogen responsible for severe respiratory disease outbreaks in 2012 in the Middle East [5]. The initial cases of SARS-CoV-19 infection were reported in early December 2019, in Wuhan, Hubei Province of China in, and related to a seafood market [6].

The infection caused by SARS-CoV-2 is transmitted by person-person contact via respiratory droplets by sneezing, coughing, talking or touching infected surfaces [7,8]. The clinical symptoms of COVID-19 patients differ from mild to moderate even to dead. The most common symptoms include dry cough, fatigue, fever, myalgia, headache, diarrhea, and respiratory failure and acute respiratory distress syndrome (ARDS). In addition, post-acute COVID-19 syndrome or long-COVID symptoms such as fatigue, brain fog, body aches, and loss of smell may persist for months [9].

According to World Health Organization (WHO) report, more than 100 million (123,419,065) people worldwide has infected and 2.7 million were dead [10]. COVID-19 pandemic has led to dead millions of people around the world. According to a study done by Matta Sh, et al in 2020, The United States had taken the number 1 by over 4 million cases with over 150 million dead. Spain, Italy and UK are other countries with high mortality rate. In Spain 253,056 cases and 28,401 deaths. Followed by Italy with 242,363 cases and 34,926 deaths. In India there were 793,802 cases, 21,604 deaths and a Fatality rate of 3.02%. Brazil with 1,713,160 cases and 67,964 Deaths. Fatality rate was 4.3% [11].

Coronavirus disease 2019 (COVID-19) outbreak, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a real challenge for health-care systems worldwide. The most common co-morbidities of COVID-19 was Hypertension rather than other co-morbidities such as diabetes, coronary heart diseases and other factors. The fact that the severity and mortality of COVID-19 infection is higher in elder people. The first explanation is that Hyperion is more common in elderly age group as well as COVID-19 severity in elderly people. another explanation for this co-morbidity is end-organ damage in hypertensive patients. Long term hypertension causes a number of pathophysiological changes in cardiovascular system such as left ventricular hypertrophy. Also having a history of cardiovascular

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diseases and risk of developing raised troponin suggest a causal relationship between hypertension and COVID-19 outcome and this may make a hypertensive patient susceptible to SARS-CoV-2. [12]

Recent studies shown that SARS-CoV-2 patients whom their hypertension were treated with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) has sever condition and were at risk of dead.

Mechanism of Action

ACE2 has been demonstrated to be a SARS-CoV-2 cellular entry receptor that CoV-19 bind to it [13]. ACE2 is the only human homolog of ACE, was first discovered in 2000, mainly in the heart, kidney, and testis and then discovered in the lungs, blood vessels, small intestine, and brain [14]. It is also expressed mainly by the epithelia of the human airway, kidneys and gastrointestinal system [15]. Patients that are treated with angiotensin-converting enzyme (ACI) inhibitors and angiotensin receptor blockers (ARBs) and because these two medicines increase ACE2 in lungs has confused scientists either it is beneficial or dangerous to COVID-19 patients. ACE2 increase SARS –CoV-2 binding to lung cells lead to increase lung injury. Angiotensin II (Ang II) is a hypertensive hormone with vasoactive, vasoconstrictive and inflammatory properties. Angiotensin II (Ang II) is a vasoactive peptide with vasocon- strictive and inflammatory properties, is regarded as a potent hypertensive hormone. There is two opposite axis to regulate RAAS, ACE/Ang II/Ang II type 1 receptor (AT1R) axis plays a positive role in regulating RAAS whereas The ACE2/Ang (1-7)/AT2R axis negatively regulates RAAS. Ang I converts into Ang II by ACE and Ang II stimulate the release of aldosterone in increase blood pressure. Ang II also induce vasoconstriction by activating AT1R. By contrast, ACE2 counteracts the action of ACE. ACE2 metabolizes Ang I and Ang II into Ang (1-9) and Ang (1-7), and both Ang (1-7) and Ang (1-9) bind and activate the Ang II type 2 receptor (AT2R), decrease blood pressure and cause vasodilation. Ang (1-7) also play a protective role in some target organs and reduce cardiac hypertrophy and pathological cardiac remodeling, preventing the occurrence of heart failure after myocardial infarction by binding to MAS receptors. [16].

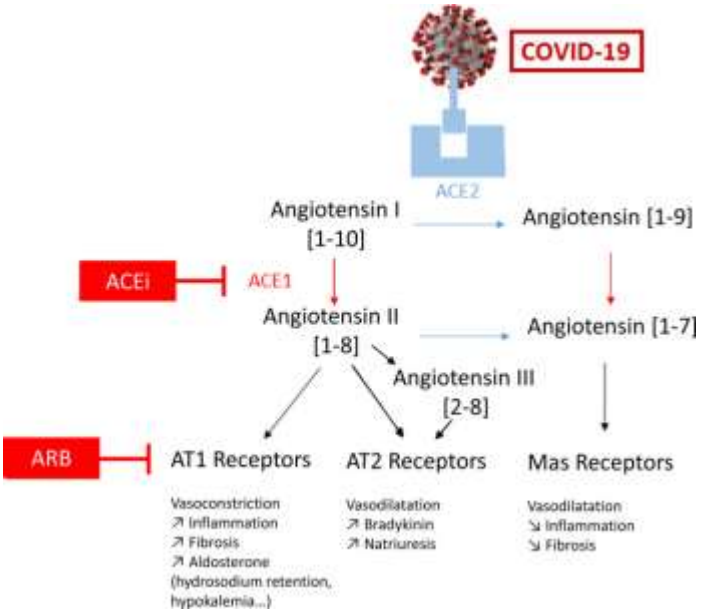

Figure 1. RAAS (renin-angiotensin-aldosterone system) and COVID-19 complication; ACEi: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin ii receptor blocker, ACE2: angiotensin-converting enzyme 2

The ACE/Ang II/AT1R and ACE2/Ang (1-7)/AT2R axis are coexpressed in some tissues, including the lung, kidney, and heart. The balance between them is important for maintaining normal physiological functions. However, ACE2/Ang (1-7)/AT2R deactivation or ACE/ Ang II/AT1R activation results in target organ damage. [17]. Both ACEI and ARBs that are used for hypertensive patients increase ACE2 level. ACEI reduce producing of Ang II whereas ARBs prevent binding of Ang II with AT1R. ACE2 has dual role in hypertensive patients, in one hand RAAS (Renin angiotensin aldosterone system) have a protective role in heart failure, kidney impairment and lungs injuries and on the other hand by increasing of ACE2 binding of SARS-CoV 2 to human cells are increased [18,19].

Some studies implied that RAAS inhibitors increase mortality rate of COVID-19 patients but some is disagreeing and the question that RAAS inhibitors are beneficial to COVID-19 patients or exacerbate disease become a hot debate. However, there is no doubt that hypertension increases the severity and mortality of COVID-19 and that a higher prevalence of hypertension is predictive of a worse prognosis in patients with COVID-19 [20,21,22]. Thus, there is insufficient evidence that RAAS inhibitors should be discontinued for the treatment of hypertension with COVID-19.

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Pathogenisis

The entry of SARS-CoV-2 into cells is a complicated process that includes receptor binding and virus-cell fusion [23]. Corona virus is composed of 4 structural proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins [5]. Among them, S protein has an important role in virus attachment and entry [13,14,15]. Spike proteins are enveloped-anchored proteins which contains of two proteins; S1 and S2 [27]. SARS-CoV-2 binds its S protein to the ACE2 receptor in the S1 domain through it's RBD and mediates membrane fusion through the S2 subunit [28]. After binding with ACE2, Interaction of host proteases such as transmembrane protease serine 2 (TMPRSS2), TMPRSS-4 , cathepsin, trypsin or human airway trypsin- like protease (HAT) with S protein and ACE2 facilitate entering the virus to the target cell [28,29]. Moreover, the availability of proteases on target cells largely determines whether coronaviruses enter cells through the plasma membrane or by endocytosis [30]. However, the specific proteases that promote virus entry into SARS-CoV-2 remain elusive [28,29].

In addition, heparin sulfate (HS) play an important role as a co-receptor on the surface of host cell for S protein binding cells. Through receptor binding domain (RBD), HS interact with ectodomain of S protein and HS activate the RBD due to starctural changes in it. Thus, HS has an important role in virus entry [27].

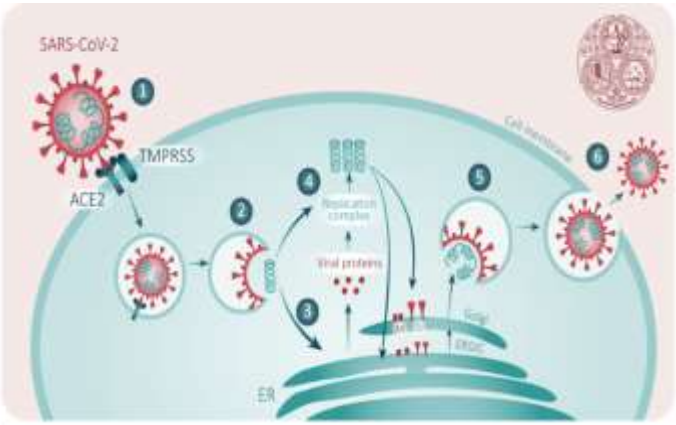

Figure 2. COVID-19 entry and replication in Human cell. Ward, P et al. (2020), 'COVID-19/SARS-CoV-2 Pandemic', Faculty of Pharmaceutical Medicines blog, 6 April. Available at: https://www.fpm.org.uk/blog/covid-19-sars-cov-2-pandemic/ (Accessed: <dare>).

After endocytosis and virus entry, the viral partial is uncoated and it genome enters the cell cytoplasm. Coronaviruses have an RNA genome from which they can directly produce their proteins and new genomes in the cytoplasm by attaching to the host ribosomes [31]. The host ribosome translates viral RNA into RNA polymerase and then into generate single-stranded, sense RNA (ssRNA+) strands. Endoplasmic reticulum makes structural component from this ssRNA+ strands and transferred to Golgi apparatus and in there ssRNA+ genome is packaged in nucleocapside to make new virus. New viruses are excreted from host cells by exocytosis to infect other cells [32]. Infected cells activated immune response and release pro-inflammatory cytokines and lead cytokine storm. Through this processes, activation of innate and adaptive immune cells such as macrophages, Natural killer (NK) cells, and gamma-delta T (γδ T) cells promote cytokine storming [33].

In sever COVID-19 disease, lymphocytopenia occur which immune cells such as CD4+ T cells, CD8+ T cells, natural killer cells, and B cells are increased in blood circulation [34,35]. Infected cell lead to activate CD4+ T cells, which differentiate into Th1 cells which secrete pro-inflammatory cytokines such as IL-6, γ-IFN (interferon), and GM-CSF (granulocyte-macrophage colony stimulating factor) and results in cytokine storm and cause acute respiratory distress syndrome (ARDS), organ failure or even death [36]. Tumor necrosis factor (TNF)-α and IL-1β are pro-inflammatory cytokines that cause an increase in vascular permeability, and induce recruitment of more immune cells, including neutrophils and monocytes. They bind to adhesion proteins on the surface of tissues and enter the site of injury [37]. Neutrophils are recruited by IL-8, and other chemokines attract monocytes [38].

Interstitial and pulmonary edema are the result of the increased in vascular permeability caused by leakage of fluid into the interstitial space and alveoli. Pulmonary edema leads to, impaired oxygenation, dyspnea or hypoxemia [39]. Inflammatory mediators, including arachidonic acid metabolites such as leukotrienes and prostaglandins are released by leukocytes and endothelial cells, leukotrienes caused hypoxemia due to bronchoconstriction [40]. Prostaglandins cause fever in assistance with IL-1, IL-6 and TNF-α [41].

Neutrophils are the first presented leukocytes in infected sites and neutrophils infiltration in lungs are taken place in severe COVID-19 [16]. Neutrophils can phagocyte pathogens or form neutrophil extracellular traps (NETs) to remove them. NETs may kill microorganisms and damage host tissue of COVID-19 patients and promote lung apoptosis. On the other hand, NETs facilitate thrombi formation and cytokine production and lead to thrombus formation and disseminated intravascular coagulation [42]. High circulating levels of

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cytokines can activate macrophages, two kinds of macrophages, alveolar macrophages (M1) and interstitial macrophages (M2) are found in lungs. M1 macrophages which activated by PAMPs enhanced recruitment of immune cells to lungs, M2 macrophages however inducing the release of anti-inflammatory cytokine which have opposite effect [43]. Because ACE2, furin and TMPRSS2 are expressed on macrophages, SARS-CoV-2 can infect macrophages and drive invasion in lungs [44]. Innate immune acts as the first defense line against the virus [45]. Hyper- activation of innate immune responses and aberrant cytokine production are associated with higher morbidity and mortality in COVID-19 infection [46].

Adaptive immunity Adaptive immunity is triggered through activation of T lymphocytes by a mechanism known as antigen presentation by Antigen Presenting Cells (APCs) [47].

APCs present structural (spike and nucleo-capsid) and non-structural (ORF3a and ORF7) protein antigens of SARS-CoV-2 and prime activation of T cells in mediastinal and cervical lymph nodes [48,49].

In addition to S protein, viral nucleocapsid protein and nonstructural viral proteins such as viral cysteine-like protease may increase titer of IgG, IgM and IgA antibody responses [50].

In hypertensive patients, hypertension develop acute cardiac inflammatory response and because the amounts of circulating monocytes, macrophages, CD8+ T cells, and CD4+ T cells are increased in heart, this lead to increase immune cell infiltration in the myocardium [51,52]. Ma et al implied that CD8+ T cells stimulate an immune response to hypertension, secreted IFN-g, and increase the amount of macrophage in the myocardium [52]. Patients with hypertension have immune dysfunction with higher levels of CRP, procalcitonin, IL-10 and IL-6 and lower CD8+ cell counts. These patients showed high levels of white blood cells and neutrophils and lower levels of lymphocytes. Thus, immune dysfunction can assist in poor outcome in COVID-19 patients and exacerbate disease [36].

COVID-19 and Hypertension

Hypertension is the most common comorbidities observed in patients infected with SARS-CoV-19 [56, 53]. Early reports from china shows that the hypertension, diabetes mellitus, heart diseases were pre-existing conditions in in patients with COVID-19. In a Retrospective, single-center case series of the 138 consecutive hospitalized patients with COVID-19, from 138 patients, 64 (46.4%) had 1 or more comorbidities. Hypertension (43[31.2%] patients), diabetes (14[10.1%]), cardiovascular- disease (20[14.5%]), and malignancy (10[7.2%]) [54]. According to a report by the Chinese center for disease control and prevention from 44,672 laboratory confirmed cases, comorbidities were hypertension (12.8%), diabetes (5.3%), cardiovascular disease (4.2%) and respiratory disease (2.4%) [55]. In other study conducted in Wuhan, china, from 710 patients, 52 (7%) was critically ill and most patients had organ damage, including 35 (67%) with Acute respiratory syndrome distress and 12 (23%) had cardiac injury which complicated with pulmonary hypertension [56]. Another study in a hospitalized patient in Wuhan, china reveals the comorbidities as diabetes 20%, hypertension 15% and cardiovascular disease 15% [57]. In other retrospective, multicenter cohort study from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China), 191 patients from 2 hospitals were included in this study. 48% of patients had comorbidities and Hypertension were the most common comorbidity (30%), diabetes (19%) and coronary heart disease (8%) [58]. In other study from china, hypertension (16.9%), diabetes (8.2%) and cardiovascular disease (3.7%) [59]. In a retrospective, observational cohort study conducted in Lombardy, Italy, of 3988 patients, the medium age was 63; 3188 patients were men, 1998 out of 3300 patients had at least 1 co-morbirbidity. Hypertension was the most comorbidity (42.1%), hypercholesterolemia (16.5%) and heart disease (16.2%) [60].

In an observational study conducted in a cohort of 12,594 patients in New York City, hypertension was reported in a 34.6% [61].

In contrast, based on the results of some studies, RAAS blockers are not harmful even it can be continued by COVID-19 patients. In a population study conducted in Lombardy region of Italy, the use of RAAS inhibitors was more frequent among 6227 compared to 30,759 controls, and suggest that the use of RAAS inhibitors/ARBs are not associated with COVID-19 severity [62]. In another papulation-based study conducted by de Abajo et al in Spain on 1139 COVID-19 patients and on 11,390 matched controls, the use of RAAS inhibitors was not associated to an increased risk of infection [63]. In a Korean study, 950 out of 16,281 hypertensive patients experienced COVID-19 disease and patients who were treated with ACEIs or ARBs didn't show risk of severity of infection [64]. In another papulation-based study in UK on 16,866 COVID-19 cases and 70,137 matched controls, to evaluate case-mortality of patients using different antihypertensive drugs. The study suggests that there is no evidence that antihypertensive therapy associated with risk of severity or mortality [65]. In another study conducted by Ibrahim Kocayigit and colleagues in Sakarya Education and Research Hospital, Turkey 169 consecutive patients were

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included and it suggests that the type of antihypertensive drugs being used had no effect on clinical outcomes and should be continued for the treatment of hypertension [66].

CONCLUTION

Based on the results of the current study, even though hypertension is one of the most common co-morbidities of severity of COVID-19 infection and it is often present in COVID-19 patients, there is no evidence that antihypertensive drugs have independent role on severity of disease. Thus, specific mechanisms that enable an understanding of how hypertension accelerates the pathogenesis of COVID-19 and how ACEIs/ARBs affect the outcomes of COVID-19 patients with hypertension deserve further investigation. Finally, many knowledge gaps remain to fill up with regard to the overall impact of hypertension on SARS-CoV-2 infection and on post-COVID syndrome and long-COVID.

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Declaration of conflicting interests

No conflict of interest

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