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Exacerbation of COVID 19 in Hypertensive Patients
（ A review ）

Noor H. Naser*,[1] and Ammar Abdul Aziz Alibeg*

* Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Kufa.

Abstract

Since its discovery in December 2019, corona virus was outbreak worldwide with a very rapid rate, so it described by World Health Organization (WHO) as a pandemic. It associated with severe acute respiratory distress syndrome, and can invade the cells through Angiotensin Converting Enzyme 2 (ACE 2) receptor which play an important role as regulator for blood pressure. Hypertension is a potential risk factor for sever acute respiratory syndrome COVID-19, and associated with high mortality rate as shown in many epidemiological studies. A lot of published article reviews, retrospective and meta-analysis regard the association between COVID-19 and hypertension. Moreover, specific antihypertensive medications that infected patients were receiving are not known; only data about renin-angiotensin-aldosterone system (RAAS) are available.

Objective: To summarize the most updated data of COVID-19 in hypertensive patients.

Keywords: COVID-19, hypertension, Angiotensin Converting Enzyme 2 (ACE2)

تفاقم COVID 19 في مرضى ارتفاع ضغط الدم

نور هاتف ناصر*،[١] و عمار عبد العزيز علي بيك*

*فرع الكيمياء الصيدلانية، كلية الصيدلة، جامعة الكوفة،النجف، العراق.

الخلاصة

منذ اكتشافه في ديسمبر ٢٠١٩ ، انتشر فيروس كورونا في جميع أنحاء العالم بمعدل سريع للغاية ، لذلك وصفته منظمة الصحة العالمية بأنه جائحة. يرتبط بمتلازمة الضائقة التنفسية الحادة الشديدة ، ويمكن أن يدخل إلى الخلايا من خلال مستقبل الإنزيم المحول للأنجيوتنسين ٢ (ACE 2)والذي يلعب دورًا مهمًا كمنظم لضغط الدم. ويعتبر ارتفاع ضغط الدم هو أحد عوامل الخطر المحتملة لمتلازمة الجهاز التنفسي الحادة الوخيمة COVID-19 ، ويرتبط بارتفاع معدل الوفيات كما هو موضح في العديد من الدراسات الوبائية. علاوة على ذلك ، فإن الأدوية المحددة الخافضة للضغط التي كان يتلقاها المرضى المصابون غير معروفة ؛ حيث تتوفر فقط بيانات حول نظام الرينين-أنجيوتنسين-الألدوستيرون.(RAAS)

الكلمات المفتاحية: COVID-19، ارتفاع ضغط الدم،الانزيم المحول للانجيوتنسين٢ (ACE2) .

Introduction

Coronavirus is a novel corona virus (nCOV), or called corona virus disease COVID-19 as it appear firstly in 2019 in Wuhan, China, then it is worldwide outbreak [(1,2)]. This virus belong to a family of positive single stranded RNA (+ssRNA) with a diameter ranging from (60-140 nm), Which can be classified as α, β, δ, and γ [(3,4)]. The COVID-19 is a type of β genus, which consist of outer capsule, from which a mushroom-like protein spike was projected and give the crown like shape for the virus, these structures facilitate the virus entry into host cell [(5,6)]. Figure 1 represents the structure of COVID-19.It is highly infectious disease that attack the respiratory system and cause Sever Acute Respiratory distress Syndrome. Due to the high genome similarity with SARS-CoV, (86.9%), so it is called (SARS-CoV-2) [(7)].

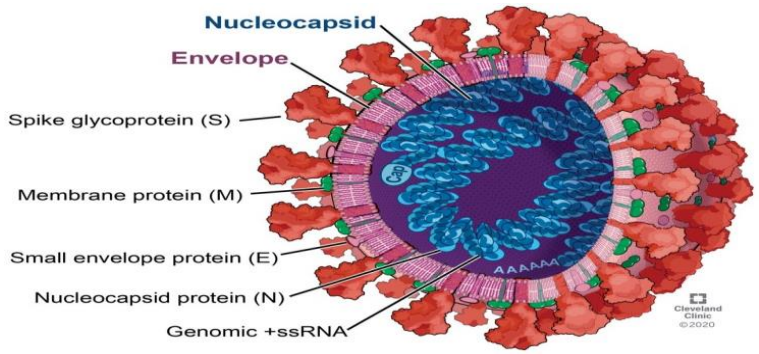

Figure 1. Structure of corona virus (8)

[1]Corresponding author E-mail: noorh.naser@uokufa.edu.iq
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Since its discovery in December 2019, the virus has transmitted at an extremely high rate around the world and was caused confusion in all joints of life, including the health and economic aspects [9].

Pathogenesis of the disease

Even though much is identified about the mortality of the disease, much less is understood about the pathophysiology of the virus. In addition the anti-inflammatory mechanisms of the virus are unclear, and much of the events can be obtained depending on the previous studies on SARS-COV [10]. According to infected cells, COVID-19 can be categorized into three different phases which are associated with different three manifestations [11].

Stage 1: Asymptomatic stage

Occurs within one to two days after the virus was inhaled, which was attached to the epithelial cells in the nasal cavity and initiate replicating through ACE2 receptor, which considered the main receptor for both SARS-COV-2 and SARS-COV [12, 13]. In this stage the virus targeted the ciliary cells [14], and this hypothesis require some clarification because single-cell RNA indicates low levels of ACE2 expression in the conduction of airway cells and no evidence predilection for the cell type [15].

Stage 2: Upper airway stage

In this stage, the virus proliferates and migrates down the respiratory tract along the conducting airways, which alert more intensive innate immune reaction. At this time the disease became clinically apparent, and the virus SARS-COV-2, should be discharged in nasal swabs and sputum secretion [16].

At this level CXCL10 (an interferon responsive gene that has an excellent signal to annoyed ratio in the alveolar type II cell responsive to both SARS-COV and influenza). Evaluating the innate immune response of the patient enhance forecasts of the disease and lead to rapid monitoring [17]. The disease may be moderate in about 80% of the infected patients, and predominantly confined to the upper and conductive airways and by ending this stage, the disease can develop into the third stage (Pneumonia). The patients with conserved symptomatic therapy may be monitored at home [18].

Stage 3: Hypoxia, ground-glass infiltration

Only 20% of the infected patients with COVID-19 will progress to stage 3, which associated with pulmonary infiltration, and some of these will be associated with very severe illness[19]. This stage associated with maximum production of pro-inflammatory and anti-inflammatory cytokines as interleukin-2 (IL2), interleukin-7 (IL7), interleukin-10 (IL10), and tumor necrotic factors-α (TNFα) [20]. At this stage the virus hits the gas exchange system of the lung and penetrate type II alveolar cells, the virus replicates and divided rapidly within these cells, and generate huge number of viral particles, then the cell induce apoptosis and perish. The outcome is possibly self-replicating pulmonary toxins, as the viral particles that generated infected type II cells in adjacent unit [21]. The pathological outcome of the virus is a wide spread alveolar injury with fibrin-rich hyaline membrane and a scare of multinucleated giant cells. The intensive scaring and fibrosis may progress to abnormal lung tissue repair [22]. Therefore an aggressive and innate immune response and epithelial regeneration will be required for rehabilitation. So, the patients with depleted immune response may permit the viral disseminate to the lung gas exchange units very readily [23].

Renin-Angiotensin-Aldosterone System (RAAS)

Renin-Angiotensin-Aldosterone System is one of the most important hormonal mechanisms that regulates the body hemodynamic, through regulation of blood pressure, fluid volume, and Na^+-K^+ balance. Therefore any disturbance in one of the system biomolecules lead to alteration in the body hemostasis and blood pressure developing [24]. Renin is a hormone synthesized in the kidney and release to the circulation in response to hypotension and low intra-tubular sodium level, this hormone responsible for conversion of Angiotensinogen to Angiotensin I (Ang I), which cleaved by Angiotensin Converting Enzyme (ACE) to give Angiotensin II [25]. Aldosterone is another biomolecule that affecting the body homeostasis, which play an important role in the reabsorption of sodium ions, potassium excretion, and water retention from the distal nephrons of the kidney, by that modulate the extracellular space volume and blood pressure [26]. Angiotensin Converting Enzyme (ACE) is a membrane bounded glycoprotein, which play an important role in the blood pressure homeostasis, through negative modulation of Renin-Angiotensin Aldosterone System (RAAS) converting of Angiotensin I into Angiotensin II, which is potent vasoconstrictor that associated with elevation in blood pressure [27].

Due to the vital role of these biomolecules in regulation of body homeostasis, therefore most patients with elevating blood pressure, and cardiovascular diseases are treated with Angiotensin Receptor Blockers (ARBs), and Angiotensin Converting Enzyme Inhibitors (ACE-I) [28], a major concern was raised about the safety and/ or persistent beneficial effects of these drugs in SARS-COVID-19 infected patients [29]. It was suggested that the binding of SARS-CoV-2 with ACE2 in hypertensive patients is an important factor for COVID-19 exacerbation and associated with increased mortality [30,31,32]. As hypertension and cardiovascular disease are important risk factors for severity and mortality in COVID-19 infected patients and considered as targets that must be intensively addressed in the management of COVID-19 [33].

Physiological Role of Angiotensin Converting Enzyme2 (ACE2)

Angiotensin Converting Enzyme-2, (ACE2) is a trans-membrane glycoprotein (mono-carboxypeptidase), which is a homologue of ACE, which responsible for conversion of Ang. II into its protective metabolites, Ang1-7 [34]. In addition it converts the angiotensin 1 into Ang1-9, which are then converted by ACE and ACE2 into Ang1-7 [35,36]. By these mechanisms ACE2 can suppress the effect of RAAS and reduce vasoconstriction and cardiac remodeling[37].

Angiotensin Converting Enzyme2 (ACE2) as Entry Receptor for COVID-19

The recent researches reported that SARS-COV2 can interact and block the ACE2, therefore they may represent a therapeutic option for COVID-19 [38,39]. The entry of the virus into the human cells occur through binding of the viral spikes with the RBD (Receptor Binding Domain) of ACE2 (Angiotensin Converting Enzyme2) [40], which is highly expressed in the type II alveolar cells and lymphocytes [41], and can be expressed in the blood vessels [42], kidney [43], and gastrointestinal tract especially (esophagus, stomach, colon [44], ileum, and rectum) [45]. This lead to internalization of ACE2 , after the binding and endocytosis of COVID 19, the ACE2 will reduce, and subsequent increase in ATII accumulation [46]. The spike protein then undergo proteolytic cleavage by trans-membrane protease serine 2 ($TMPRSS_2$) enzyme [47], which allows fusion to the cell [48]. Such binding determines viral entry and cell injury, which is directly proportional to ACE2 expression [49,50].

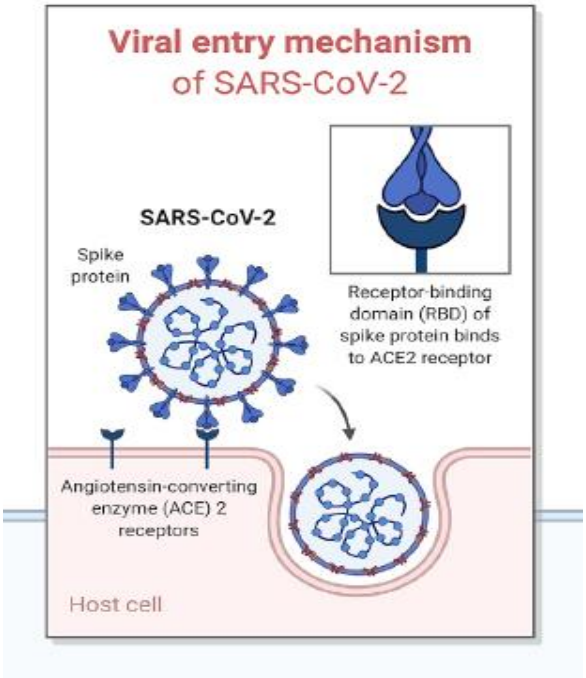

Figure 2. Role of ACE2 in the entry of COVID 19 into the host cells [51].

The Association Between Hypertension and COVID 19

The association between hypertension and COVID 19 was concern of many studies [52,53]. Since the pathogenesis of COVID 19 interact with ACE2 receptors a one of the components of Renin-Angiotensin system (RAS), which is the key of blood pressure regulation [54]. ACE2 is the receptor that mediates the invasion of COVID 19 into the cells by a spike (S) glycoprotein-ACE2 binding pathway [55]. After infection, the ACE2 level was reduced due to the binding with the spike protein of COVID 19, resulting in an imbalance between ACE1 and ACE2 [56]. The Renin-Angiotensin II-Aldosterone axis was recognized as a key regulator of blood pressure in the hypertensive patient, with Angiotensin II regulated through ACE [57]. Thus, due to imbalance between ACE1 and ACE2 result from viral infection, the hypertensive patients tend to appear more serious organs injury [58]. In hypertensive COVID 19 patients more sever clinical types of mortality were observed, leading to a suggestion that COVID 19 associated the clinical outcome of COVID 19 [59]. F. Xei et al study, found that 31% of hypertensive patients also have other forms of cardiovascular diseases, associated with increased risk of death in COVID 19 patients [60]. Accordingly, preexisting hypertension, rather than cardiovascular disease was considered the underlying cause of increased susceptibility to rapid progression of the disease, and more sever COVID 19 infection [61,62].

Wu et al. [63] and Zhou et al.[64] had found hypertension to have a hazard ratio of 1.70 and 3.05 for death in 201 and 191 patients with COVID-19, respectively. There is an important question, whether Angiotensin Converting Enzyme-Inhibitors (ACE-I), and Angiotensin Receptor Blockers (ARB), which are a group of important anti-hypertensive agents medications, have favorable impact on the patients infected with SARS-CoV-2, or associated with deleterious effect [65], because it was found that ACE-I, and ARB induced over expression of ACE2 receptors, which are facilitating the entry of the virus to the host cell, and propagation of the cell injury.

RAAS activation plays a major pathogenic role in hypertension through hemodynamic actions and cytokines and intracellular signaling pathways, which lead to adverse cellular effect result in systemic damage. Many hypothesis have been raising about which is more beneficial or should withdrawing the medications? Although the number of fatal COVID-19 positive patients treated with ACE-Is was more than twice the number of those treated with ARBs, it cannot absolutely conclude the risks or benefits of using such medications, due to the association of other factors as age, environment, and impact of unidentified comorbidities on outcome with the COVID-19 patients [66,67]. ACE2

alleviates the vasoconstriction, and pro-fibrotic effect of Angiotensin-II through its degradation and by counteracting its action through formation of Ang 1-7. The high expression of ACE2 in the cardiovascular system, type II alveolar cells, and enterocytes, demonstrates its essential role in the cardiovascular and immune systems. Sanchis-Gomar *et al* study, suggested that the usage of ARBs may be a better treatment option for hypertensive patients with COVID-9 patients at higher risk of sever forms of the disease due to the equal efficacy, but much more fewer side effects than that of ACE-Is[68,69].

G. Chao et. el. [70] and V. Muthiah [71] had found that abrupt withdrawal of ACE-I and ARBs, in high risk patients, such as those with heart failure or myocardial infarction may result in clinical instability and adverse health outcomes. So, these studies suggested that the RAAS inhibitors should be continued in patients in otherwise stable conditions who are at risk for, being evaluated for, or with COVID-19 [72,73].

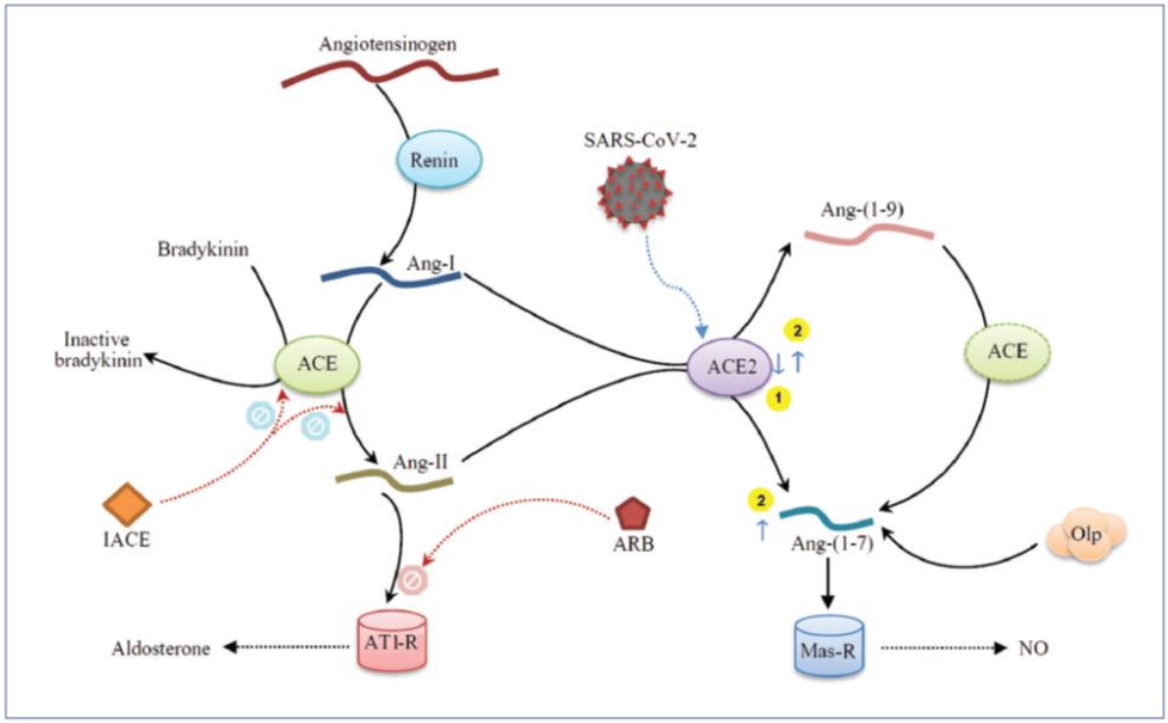

Figure 3. Effect of SARS-CoV-2 on physiological action of Renin-Angiotensin-Aldosterone- System. 1. Reduction of ACE2 during corona virus infection 2. Increase ACE2 and Ang (1-7) after ACE-Is and ARBs administration [74].

ACE: Angiotensin Converting Enzyme, ACE2: Angiotensin Converting Enzyme2, ARB: Angiotensin II Receptor Blockers, AT1-R: Angiotensin II Receptor Type I, Mas R: Mas Receptor, NO: Nitric Oxide, Olp: Oligopepidase and neprilysin (in blood circulation).

Conclusion

The entry of SARS-Cov-2 into the cells occur through Protein Binding Domain (PBD) of the ACE2 receptor, which considered as a key hormone for blood pressure regulation. ACE-I/ and or ARB were not associated with the increased risk of mortality or sever manifestations in patients with COVID-19 infection. So, the ACE2/ARB can be continued without concern of drug related worsening in patients with COVID-19. Certain studies were shown that the accidental withdrawal of ACE-Is or ARBs medication from hypertensive or heart failure patients result in clinical instability and adverse health outcome, this give the importance of continuation of such medical treatment with those patients even when infected with COVID-19.

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