Review Article

ROLE OF ANGIOTENSIN SYSTEM INHIBITION IN THE CARDIOVASCULAR MANIFESTATIONS OF COVID – 19

Muhammad Saeed Anwar[1], Mariyam Iftikhar Piracha[2]

ABSTRACT

The Association of the drugs inhibiting the angiotensin system with the severity of coronavirus disease has been studied intensively at different research centers of the world over the past year. It has been found that the admitted COVID-19 patients with co-existing cardiovascular diseases taking angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) develop less severe disease, and persistent ACEI /ARB therapy during their hospitalization lowers the risk of fatality as well. The current literature supports the use of ACEI/ARB therapy for corona patients with co-morbidities as it yields better clinical outcomes.

Key Words: COVID-19, Angiotensin-Converting Enzyme Inhibitors, Angiotensin Receptor

INTRODUCTION

Corona Virus disease (COVID-19), a pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus- 2 (SARS-CoV-2) has emerged as the most striking medical challenge of the era and is associated with a notable rise in morbidity and mortality worldwide.[1] Basically, it is a pulmonary disease but affects the cardiovascular system as well. Advancing age, male sex, and comorbidities like cardiovascular diseases, chronic pulmonary diseases, diabetes, and cancer are the major risk factors for severe infection and mortality.[2]

As Angiotensin-Converting enzyme type 2 (ACE2) is the significant receptor for the entry of the virus into the host's pulmonary cells, it was speculated that drugs modifying Renin-Angiotensin System (RAS) may increase the risk for infection and severity.[3] Therefore, it was hypothesized that Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB); the major drugs prescribed for cardiovascular diseases make patients vulnerable to corona infection and also worsen the disease outcomes through upregulation of the functional receptor essential for the virus's entry: ACE2.[4]

Thus, a great conflict about their use in COVID-19 developed and is one of the major concerns for clinicians treating COVID patients with cardiovascular diseases.

In the current review, clinical and pathological features of COVID-19 mediated damage to the cardiovascular system, the potential pathogenic role of ACE2 in COVID, factors modifying ACE2 expression and activity in relation to COVID-19, and potential therapeutic options for COVID-19 will be discussed.

DISCUSSION

Pathological and Clinical characteristics of COVID-19 mediated cardiac complications

COVID-19 has the peculiar properties of high transmission, long incubation period, and varied clinical manifestations. Besides pulmonary insult; causing Acute Respiratory Distress Syndrome (ARDS), it also involves other systems, especially the cardiovascular system (CVS).[5] The most common cardiac complications include myocarditis, arrhythmia, disseminated intravascular coagulation, pulmonary embolism, and heart failure.[6] Based on limited knowledge of the disease, the proposed process of cardiac insult involves the direct entry of the virus and myocardial injury, hypoxia, cytokine storm, systemic inflammation, interferon-

[1]Professor Pharmacology, AMDC, Lahore.
[2]Assistant Professor Pharmacology, AMDC, Lahore.

mediated immune response, and plaque destabilization.[7]

Cardiac biomarkers (D-dimer, troponin) rise frequently, particularly during the phase of systemic inflammation and ARDS, and are quantitatively associated with poor disease outcome.[8] Initially pulmonary infection may cause right ventricular dysfunction but as a consequence of cytokine storm, hypoxia, and systemic inflammation; heart failure may develop.[7] However, even mild COVID-19 infection in children can produce a multisystem inflammatory syndrome along with the cardiogenic shock.[8]

Current researches indicate that mortality from COVID-19 can be attributed to cardiovascular diseases and disease outcome worsens in patients with comorbidities like hypertension and diabetes mellitus probably due to overexpression of ACE2 receptors.[9]

Pathogenic Role of ACE2 in COVID-19:

Coronavirus enters the host cells by binding its spike proteins to ACE2 which is widely expressed in different tissues and plays a central part in disease pathogenesis.[10] ACE2 catalyses the conversion of angiotensin I (Ang I) to angiotensin II and has direct effects on the CVS and multiple organs via counter-regulation of RAS (Figure-1). The pulmonary insult by coronavirus affects both alveolar interstitium and capillaries, and is linked to functional downregulation of ACE2.[11] It is an essential enzyme for balancing the two arms of RAS: ACE/Angiotensin (Ang) II/Ang II type 1 Receptor Axis (classic RAS) and the ACE2/Ang (1-7)/ Mas- receptor axis (anti-RAS). Downregulation of ACE2 enhances the classic RAS and reduces the anti-RAS mediated attenuation leading to lung injury, leaky blood vessels, inflammation, and pulmonary fibrosis.[12] With the progression of the disease immune cells and coagulation pathways get activated leading to multiorgan failure and eventually death.[10]

Factors determining expression and activity of ACE2 in relation to COVID-19

Multiple factors have been linked to altered ACE2 expression and severity of COVID-19, including age, gender, ethnicity, comorbidities: cardiovascular diseases and metabolic syndrome, and medications.[13]

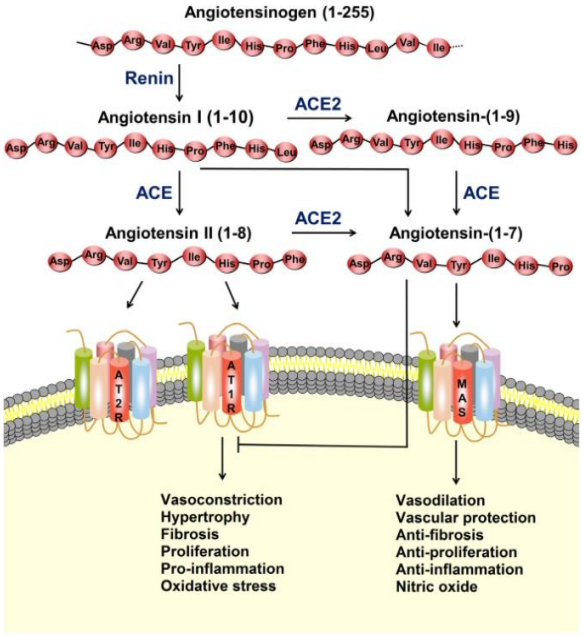

Figure-1: Renin Angiotensin System (RAS) and ACE2 / angiotensin-(1-7) MAS axis (https://ccforum.biomedcentral.com)

ACE inhibitors are a group of drugs primarily used in the management of hypertension and heart failure. They cause vasodilation and decrease blood volume, which lowers the blood pressure and reduces the cardiac oxygen demand.[14]

In vitro, both ACEIs and ARBs have been shown to upregulate the expression and activity of ACE2. Increasing ACE2 may be beneficial as it forms Ang (1-7), a vasodilator that possesses anti-oxidative and anti-inflammatory properties and thus might prevent multiorgan failure plus ACE2 blockade may disable viral entry into the heart and lungs.[15]

A study showed that ACEI or ARB therapy in comparison to other antihypertensives in COVID patients, lowered the disease severity, decreased IL-6, and increased CD3 and CD8 T cell counts in peripheral blood in addition to the reduction in peak viral load.[16] This evidence supports the usage of these drugs in COVID-19 patients with cardiovascular diseases.

Vitamin D, a fat-soluble vitamin, is a negative endocrine renin-angiotensin system modulator that induces anti-RAS axis and inhibits classic-RAS axis by increasing ACE2 and Ang-(1-7) concentration and expression and thus might prove beneficial in COVID-19 associated ARDS.[17]

CONCLUSION

The exact impact of Renin-Angiotensin System blockers on COVID-19 infection is currently unknown. There is no evidence of the detrimental effects of using angiotensin inhibitors during COVID-19 infection despite the theoretical concerns of probably increased expression of ACE2 by RAS blockade but in fact, their use has been proven favorable in some animal studies. Based on their anti-inflammatory effects and current data it can be concluded that treatment with RAS inhibitors in COVID may outweigh the risks and therefore, currently there is no reason to abort their use in COVID-19. Although for the ultimate decision, more clinical studies are mandatory to assess the safety of RAS blockers in COVID-19.

FUTURE RECOMMENDATIONS

Extensive knowledge of the cardiovascular effects of the corona virus is a prerequisite for the development of novel therapeutic strategies to target the virus-induced cardiac damage and hence reduce morbidity and mortality. ACE2 interaction with viral S protein and ACE2/Ang 1-7 axis could be potential targets for developing preventive and therapeutic regimens for COVID-19 and decreasing its severity.

AUTHOR'S CONTRIBUTION

MSA: Critical revision & final approval of article
MIP: Drafting & Editing

REFERENCES

1. Bchetnia M, Girard C, Duchaine C, Laprise C. The outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A review of the current global status. J Infect Public Health. 2020 Nov;13(11):1601-10. doi: 10.1016/j.jiph.2020.07.011
2. Khan M, Khan H, Khan S, Nawaz M. Epidemiological and clinical characteristics of coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. J Med Microbiol. 2020 Aug 1;69(8):1114-23. doi: 10.1099/jmm.0.001231.
3. Hakeam HA, Alsemari M, Duhailib ZA, Ghonem L, Alharbi SA, Almutairy E, Sheraim NM, Alsalhi M, Alhijji A, AlQahtani S, Khalid M. Association of angiotensin-converting enzyme inhibitors and angiotensin II blockers with severity of COVID-19: A multicenter, prospective study. J Cardiovasc Pharmacol Ther.2021 May;26(3):244-52. doi:https://doi.org/10.1177%2F1074248420976279
4. Fosbøl EL, Butt JH, Østergaard L, Andersson C, Selmer C, Kragholm K, et al. Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with COVID-19 diagnosis and mortality. JAMA. 2020 Jul 19;324(2):168-77. doi: doi:10.1001/jama.2020.11301
5. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 2020 Aug 25;324(8):782-93. doi: doi:10.1001/jama.2020.12839
6. Khawaja SA, Mohan P, Jabbour R, Bampouri T, Bowsher G, Hassan AM, et al. COVID-19 and its impact on the cardiovascular system. Open heart. 2021 Mar 1;8(1):e001472. doi: http://dx.doi.org/10.1136/openhrt-2020-001472
7. Kurz DJ, Eberli FR. Cardiovascular Aspects of COVID-19. Swiss Med Wkly. 2020 Dec 31;150: w20417. doi: 10.4414/smw.2020.20417.
8. Tajbakhsh A, Hayat SMG, Taghizadeh H, Akbari A, Inabadi M, Savardashtaki A, et al.COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. Expert Rev Anti Infect Ther 2021 Mar;19(3):345-57. doi: 10.1080/14787210.2020.1822737.

9. Groß S, Jahn C, Cushman S, Bär C, Thum T. SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: from basic science to clinical implications. J Mol Cell Cardiol.2020 Jul 1;144:47-53. doi:https://doi.org/10.1016/j.yjmcc.2020.04.031
10. Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, et al.Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol.2020 May 17;251(3):228-48. doi: https://doi.org/10.1002/path.5471
11. Datta PK, Liu F, Fischer T, Rappaport J, Qin X. SARS-CoV-2 pandemic and research gaps: Understanding SARS-CoV-2 interaction with the ACE2 receptor and implications for therapy. Theranostics. 2020 Jun 12;10(16):7448-64. doi: 10.7150/thno.48076
12. Sarzani R, Giulietti F, Di Pentima C, Giordano P, Spannella F. Disequilibrium between the classic renin-angiotensin system and its opposing arm in SARS-CoV-2-related lung injury. Am J Physiol Lung Cell Mol Physiol. 2020 Aug 5;319(2):325-36. doi:https://doi.org/10.1152/ajplung.00189.2020
13. Brojakowska A, Narula J, Shimony R, Bander J. Clinical Implications of SARS-CoV-2 Interaction With Renin Angiotensin System: JACC Review Topic of the Week. J Am Coll Cardiol.2020 Jun 23;75(24):3085-95. doi:https://doi.org/10.1016/j.jacc.2020.04.028
14. Dworakowska D, Grossman AB. Renin-angiotensin system inhibitors in management of hypertension during the covid-19 pandemic. J Physiol Pharmacol. 2020 Apr 1;71(2):173-8. doi: 10.26402/jpp.2020.2.01
15. Yehualashet AS, Belachew TF. ACEIs and ARBs and Their Correlation with COVID-19: A Review. Infect Drug Resist. 2020 Sep 16;13:3217-24. doi: 10.2147/IDR.S264882
16. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg microbes & infect. 2020 Mar 31;9(1):757-60. doi:https://doi.org/10.1080/22221751.2020.1746200
17. Mahdavi AM. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: Implications for a potential treatment for COVID-19. Rev Med Virol. 2020 Jun 25;30(5):e2119. doi: https://doi.org/10.1002/rmv.2119