Hypertension in COVID-19, A Risk Factor for Infection or A Late Consequence?

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Abstract

There are a lot of data about the correlation of SARS-CoV-2 infection and hypertension (HTN), but most of them are in the increased risk of morbidity and mortality in patients with HTN. SARS-CoV-2 can interfere with host cells through the renin-angiotensin system (RAS) via the angiotensin-converting enzyme 2 (ACE2) receptor. RAS activation is associated with pro-inflammatory effects through the ACE/Ang II/ Angiotensin II type 1 receptor (AT1R) pathway or anti-inflammatory effects through ACE2/Ang1-7/Mas axis. In the current paper, we discuss the pathophysiology of newly diagnosed HTN and its effect on morbidity in patients with coronavirus disease 2019 (COVID-19).

Keywords: COVID-19, Hypertension, Renin-Angiotensin-Aldosterone System

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) firstly reported in Wuhan in 2019 (1), China, that caused more than 517 million confirmed cases and almost 6.2 million deaths until 6 May 2022 (2). It is shown that cardiovascular diseases and risk factors such as hypertension (HTN) are associated with more severe symptoms in affected individuals including dyspnea, and hypoxia. These patients need intensive care unit (ICU) that represent the increased likelihood of morbidities, and even mortality (3). On the other hand, HTN may be a consequence of COVID-19, due to the over-activity of the renin-angiotensin system (RAS) (4).

During the COVID-19 pandemic disease, especially during lockdown and quarantine, diagnostic and therapeutic interventions for HTN were reduced significantly, which deteriorates the long-term consequences of HTN and cardiovascular events (5, 6). In addition, studies reported that the COVID-19 pandemics has changed the treatment strategies of HTN in order to have a better management of this condition in patients (7). In this study, we review the association between COVID-19 and HTN as a risk factor for the infection, and a consequence of the infection.

COVID-19 and RAS

SARS-CoV-2 penetrates host cells using surface spike protein through the angiotensin-converting enzyme 2 (ACE2) receptor that interferes with host cells via RAS (8). Recent studies showed that RAS over-activation might have pro-inflammatory, profibrotic, and vasoconstrictive effects by reactive oxygen species (ROS) production and cytokines release through ACE/Ang II/ Angiotensin II type 1 receptor (AT_1R) pathway (9). However, RAS can act through an alternative pathway, the ACE2/Ang1-7/Mas axis, which is a counter-regulator of classic pathway causing anti-inflammatory effects (10). It was revealed that, the ACE2/Ang1-7/Mas axis, may be downregulated in COVID-19 infection due to eliminating ACE2 expressing cells by virus. This issue may cause the over expression of ACE/Ang II/AT_1R pathway (11). Since angiotensin II receptor blockers, ACE inhibitors, and mineralocorticoid receptor antagonists overexpressed the ACE2 receptor, it has been thought that these drugs can lessen the severity of the disease and cause ACE2/Ang1-7/Mas axis upregulation. These properties associated with beneficial effects on lung function. Therefore, these drugs should not be withheld during COVID-19 (12).

Inflammation

SARS-CoV-2 infection can induce cytokine storm via different mechanisms. The activation of Ang II, which promotes production of pro-inflammatory cytokines such as IL-6 and TNF-alpha causing an influx of inflammatory cells to the infected sites

results in vascular injury, fibrosis and even thrombosis (13). In addition, SARS-CoV-2 infection can induce production of ROS, which stimulates the synthesis of NF-κB (14). This usually results in increment of cytokines and the cytokine storm (15). On the other hand, the role of inflammation in HTN has been investigated. It seems that systemic inflammation may cause arterial stiffness associated with elevating blood pressure until the rage of HTN (16). In fact, oxidative stress alongside chronic inflammation causes changing the arterial walls, increase in intima-media thickness, and endothelial dysfunction (17).

It was shown that endothelial dysfunction may be associated with essential HTN (18) and severe endothelial injury in the severe COVID-19 (19). It seems that endothelial dysfunction resulted from HTN, may exacerbate COVID-19 symptoms in patients with HTN; also, and in some patients without HTN, endothelial dysfunction resulted from COVID-19 infection may develop HTN in near future.

Hypertension: a risk factor for COVID19 or its consequence?

The endothelial dysfunction caused by HTN may influence the outcome of COVID-19. In the evaluation of newly onset HTN in COVID-19, there are many of studies that supported this concept. In a study in late 2021 on 211 COVID-19 patients, new onset HTN was seen in 18 patients during a 30-day follow-up (20). In another study by Chen et al. (4) on 366 patients, new onset HTN was observed in 190 patients without history of HTN, with high levels of Ang II and cardiac troponin. In addition, Bekbossynova et al. (21) observed a case of COVID-19 that was manifested as sudden HTN. However, conflicting results observed in a cohort study in China on more than 1,700 COVID-19 patients with a six months follow-up, without reports of newly diagnosed HTN (7).

According to our explorations, there is a close relationship between HTN and COVID-19 infection. Each of them can induce and exacerbate the other one; although, more studies are needed to investigate new onset HTN after COVID-19.

How should we battle?

It was suggested that the mortality rate is similar in adjusted model analysis, in the context of beta blocker, ACEIs or ARBs consumption in COVID-19 patients (22). Furthermore, large scale studies reduced the uncertainties in the context of medication controversies in COVID-19 patients with HTN; however, further cohort studies are needed to confirm this hypothesis.

Conclusion

According to our explorations, there is a close association between HTN and COVID-19 infection. Each of them can induce and exacerbate the other one; although, to have a better insight, more studies are needed to investigate new onset HTN after COVID-19.

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Authors' Contributions

M.B., M.V.; Contributed to conception and design. M.A.S., K.R.; Drafted the manuscript, which was revised by M.B. and M.V. All authors read and approved the final manuscript.

References

1. Available from: https://covid19. who.int/ (13 May 2022).
2. Shahrbaf MA, Hassan M, Vosough M. COVID-19 and Hygiene Hypothesis: increment of the Inflammatory Bowel Diseases in next generation? Expert Rev Gastroenterol Hepatol. 2022; 16(1): 1-3.
3. Savoia C, Volpe M, Kreutz R. Hypertension, a moving target in COVID-19: current views and perspectives. Circ Res. 2021; 128(7): 1062-1079.
4. Chen G, Li X, Gong Z, Xia H, Wang Y, Wang X, et al. Hypertension as a sequela in patients of SARS-CoV-2 infection. PLoS One. 2021; 16(4): e0250815.
5. Weber T, Amar J, de Backer T, Burkard T, van der Giet M, Gosse P, et al. Covid-19 associated reduction in hypertension-related diagnostic and therapeutic procedures in Excellence Centers of the European Society of Hypertension. Blood Press. 2022; 31(1): 71-79.
6. Burnier M, Kjeldsen SE, Narkiewicz K, Egan B, Kreutz R. Hypertension management during the COVID-19 pandemic: what can we learn for the future? Blood Press. 2022; 31(1): 47-49.
7. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021; 397(10270): 220-232.
8. Yang J, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, Chen W, et al. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. Nat Commun. 2020; 11(1): 4541.
9. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010; 2(7): 247-257.
10. Capettini LS, Montecucco F, Mach F, Stergiopulos N, Santos RA, da Silva RF. Role of renin-angiotensin system in inflammation, immunity and aging. Curr Pharm Des. 2012; 18(7): 963-970.
11. Issa H, Eid AH, Berry B, Takhviji V, Khosravi A, Mantash S, et al. Combination of angiotensin (1-7) agonists and convalescent plasma as a new strategy to overcome angiotensin converting enzyme 2 (ACE2) inhibition for the treatment of COVID-19. Front Med (Lausanne). 2021; 8: 620990.
12. 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; 75(24): 3085-3095.
13. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol. 2020; 20(6): 363-374.
14. Shahriari-Felordi M, Alikhani HK, Hashemian SM, Hassan M, Vosough M. Mini review ATF4 and GRP78 as novel molecular targets in ER-Stress modulation for critical COVID-19 patients. Mol Biol Rep. 2022: 1-5.
15. Bhaskar S, Sinha A, Banach M, Mittoo S, Weissert R, Kass JS, et al. Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper. Front Immunol. 2020; 11: 1648.

16. Tomiyama H, Shiina K, Matsumoto-Nakano C, Ninomiya T, Komatsu S, Kimura K, et al. The contribution of inflammation to the development of hypertension mediated by increased arterial stiffness. J Am Heart Assoc. 2017; 6(7): e005729.
17. Castellon X, Bogdanova V. Chronic inflammatory diseases and endothelial dysfunction. Aging Dis. 2016; 7(1): 81-89.
18. Faulkner JL, Belin de Chantemèle EJ. Mineralocorticoid receptor and endothelial dysfunction in hypertension. Curr Hypertens Rep. 2019; 21(10): 78.
19. Ruhl L, Pink I, Kühne JF, Beushausen K, Keil J, Christoph S, et al. Endothelial dysfunction contributes to severe COVID-19 in combination with dysregulated lymphocyte responses and cytokine networks. Signal Transduct Target Ther. 2021; 6(1): 418.
20. Akpek M. Does COVID-19 cause hypertension? Angiology. 2021: 33197211053903.
21. Bekbossynova M, Ainur T. Hypertension as a manifestation of COVID-19 pneumonia. Clin Case Rep. 2021; 9(9): e04720.
22. Tadic M, Saeed S, Grassi G, Taddei S, Mancia G, Cuspidi C. Hypertension and COVID-19: ongoing controversies. Front Cardiovasc Med. 2021; 8: 639222.