Blocking angiotensin earlier with RAS blockers, statins, and heparin in high-risk COVID-19 patients: Is the remedy here?

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Introduction

Early data about the coronavirus disease 2019 (COVID-19) showed that older male patients with hypertension and diabetes mellitus were more likely to die of COVID-19 (1). This was linked to the fact that the virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor. Some medical experts question the safety of using angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) among COVID-19 patients because ACE2 levels are increased in patients who are on ACEI/ARBs treatment (2). However, some recently published papers hypothesized that ACEI and ARBs might be even beneficial in COVID-19 patients, since ACE2 decreases the level of angiotensin 2 (AT2) (3, 4). We also hypothesized that the catastrophic clinical picture in susceptible patients could be as a result of increased AT2 levels. In this paper, we discussed whether early use of well-known drugs that have some inhibitory effects on AT2 such as ACEI/ARB, statins, and heparin could reverse AT2 effects on the body.

ACE2, an ACE homolog, converts AT2 to angiotensin (1–7), thereby diminishing the potent vasoconstrictor effect of AT2 (5). We also know that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses ACE2 as a receptor for entry into the cell. The question in mind is whether high levels of ACE2 increase the severity of infection? Xudong et al. evaluated ACE2 in rats and showed that ACE2 levels were diminished in old and male rats (6). It is expected that low levels of ACE2 are present in older male patients who have the worst clinical course in COVID-19. Although diminished ACE2 levels decrease the chance of virus' entry into the cell, once the virus endocytosis occurs, the surface ACE2 is further suppressed, resulting in AT2 accumulation (3). Increased levels of AT2 augment the local and systemic renin-angiotensin aldosterone system (RAAS) and this could be the main trigger point of the whole bad scenario.

ACE2 is found most abundantly in the lungs, heart, kidney, endothelium, and intestines (7). Lungs are the most frequent target of the SARS-CoV-2. When lung cells are infected, decreased ACE2 levels result in unopposed AT2. Upregulated AT2 causes pulmonary artery vasoconstriction, disrupted vascular permeability secondary to hypoxia, secretion of inflammatory cytokines, accelerated apoptosis, stimulation of extracellular matrix production, and lung fibroproliferation (8). Therefore, increased AT2 levels in the lungs can explain the similar pathological processes seen in acute respiratory distress syndrome (ARDS) and hypoxic conditions such as COVID-19. On the other hand, a recent study showed that COVID-19 causes endothelial infection and endothelitis (9). It is expected that when the virus enters the endothelium via ACE2, unopposed AT2 levels secondary to decreased ACE2 activity enhances inflammatory processes and vascular remodeling and exacerbates vasoconstriction and endothelial inflammation by decreasing NO production on the damaged endothelium. It is also known that AT2 increases the *in vivo* IL-6 level that could support the cytokine storm seen in COVID-19 patients. Additionally, AT2 enhances plasminogen activator inhibitor-1 (PAI-1) expression and causes a procoagulant situation (10). It has shown increased PAI-1 levels seen in ARDS in relation with worse prognosis (11). All these could explain the severe procoagulant situation in COVID-19 patients.

Heparin, a commonly used anticoagulant, inhibits AT2-related vasoconstriction via cAMP-dependent pathways (12). Heparin also inhibits neutrophil chemotaxis and binds cytokines, so that the early usage of heparin in high-risk COVID-19 patients could be appropriate before AT2 dominancy occurs.

Moreover, statins are lipid-lowering, antioxidant, and anti-inflammatory drugs that also increase the NO secretion and ef-

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fect. Statins decrease AT2 synthesis, AT1 receptor levels, and aldosterone synthesis by reducing RAAS activation. As a result, statins reduce AT2-related intracellular signaling, oxidative stress, and inflammation (13).

Conclusion

Although it should be supported by clinical experiments and trials, we hypothesized that unopposed AT2 levels secondary to reduced ACE2 expression may be the main trigger of the catastrophic clinical consequences in COVID-19 patients, especially among hypertensive and diabetic patients who have damaged endothelium and older male patients who have lower ACE2 levels. Suppressing AT2 effects by using intense ACEI/ARBs (preferably ARBs because of less prominent coughing side effect), statins, and heparin, especially in high-risk patients, should be considered in the early period of the disease before AT2 dominancy occurs.

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References

1. Leung C. Clinical Features of Deaths in the Novel Coronavirus Epidemic in China. Rev Med Virol 2020; 30: e2103. [CrossRef]
2. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? JAMA 2020; doi: 10.1001/jama.2020.4812. Epub ahead of print [CrossRef]
3. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med 2020; 382: 1653-9. [CrossRef]
4. AlGhatrif M, Cingolani O, Lakatta EG. The Dilemma of Coronavirus Disease 2019, Aging, and Cardiovascular Disease: Insights From Cardiovascular Aging Science. JAMA Cardiol 2020; doi: 10.1001/jamacardio.2020.1329. Epub ahead of print [CrossRef]
5. Varagic J, Ahmad S, Nagata S, Ferrario CM. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Version 2. Curr Hypertens Rep 2014; 16: 420. [CrossRef]
6. Xie X, Chen J, Wang X, Zhang F, Liu Y. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci 2006; 78: 2166-71.
7. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631-7. [CrossRef]
8. Zhang H, Baker A. Recombinant human ACE2: acing out angiotensin II in ARDS therapy. Crit Care 2017; 21: 305. [CrossRef]
9. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395: 1417-8. [CrossRef]
10. Watanabe T, Barker TA, Berk BC. Angiotensin II and the endothelium: diverse signals and effects. Hypertension 2005; 45: 163-9.
11. Capelozzi VL, Allen TC, Beasley MB, Cagle PT, Guinee D, Hariri LP, et al. Molecular and Immune Biomarkers in Acute Respiratory Distress Syndrome: A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med 2017; 141: 1719-27. [CrossRef]
12. Xie-Zukauskas H, Das J, Short BL, Gutkind JS, Ray PE. Heparin inhibits angiotensin II-induced vasoconstriction on isolated mouse mesenteric resistance arteries through Rho-A- and PKA-dependent pathways. Vascul Pharmacol 2013; 58: 313-8. [CrossRef]
13. Koh KK, Sakuma I, Hayashi T, Kim SH, Chung WJ. Renin-angiotensin system inhibitor and statins combination therapeutics - what have we learnt? Expert Opin Pharmacother 2015; 16: 949-53. [CrossRef]