

SHORT PERSPECTIVE

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Bradykinin as a Probable Aspect in SARS-Cov-2 Scenarios: Is Bradykinin Sneaking out of Our Sight?

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ABSTRACT

The new virus SARS-CoV-2 is savagely spreading out over the world. The biologic studies show that the target receptor for the virus might be angiotensin-converting enzyme 2 (ACE2). This peptide is responsible for converting angiotensin II (Ang II), which is a profoundly active peptide, into Ang 1-7 with quite a balancing barbell function. It is emphasized that the direct target of the virus is ACE2 underlining the obvious difference with ACE. Nevertheless, we hypothesized that a back load build up effect on Ang II may usurp the ACE capacity and subsequently leave the bradykinin system unabated. We think there are clinical clues for dry cough and the presumed aggravating role of ACE inhibitors like captopril on the disease process. Thereby, we speculated that inhibition of bradykinin synthesis and/or blockade of bradykinin B₂ receptor using Aprotinin/ecallantide and Icatibant, respectively, may hold therapeutic promise in severe cases and these molecules can be advanced to clinical trials.

Keywords: Aprotinin; Angiotensin-converting enzyme 2; Bradykinin; Icatibant; SARS-CoV-2

INTRODUCTION

Severe respiratory sickness was first reported in Wuhan city, Hubei province in China, and on January 30, 2020, the world health organization

(WHO) confirmed the Chinese outbreak of COVID-19 as a public health emergency.^{1,2} Although COVID-19 may only cause mild symptoms (dry cough, sore throat, and fever) with spontaneous recovery, in some cases it is associated with life-threatening situations such as organ failure, septic shock, pulmonary edema, severe pneumonia, and acute respiratory distress syndrome.³ Notably, the emergency of the

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situation, rapidly growing burden of the disease, and its paralyzing consequences on societies are a clear depiction of “reality” making it difficult to endure with solemnity and precision. At the time, despite applying intensive supportive regimens to control the severity of the illness in COVID-19 patients, respiratory failure due to the respiratory distress syndrome remains as the main cause of mortality.⁴ Given this, achieving biologic hypothetical frames in this situation is of utmost importance for designing effective treatments. In this excerpt, we try to allude toward a familiar scenario based on the interaction of the renin-angiotensin system with the bradykinin system upon coronavirus attack. At the inception of writing our work, we did not find any hint or postulation of its role in the previous literature. We may still have no facts but we can raise and shed a light on a corner that has not been yet illuminated.

Bradykinin as a potent vasodilator autacoid peptide is widely distributed in plasma and different tissues. It is produced via enzymatic activity of kallikrein on the low molecular weight and high molecular weight kininogens, respectively, in tissues as well as plasma and is degraded by both angiotensin-converting enzyme (ACE) and carboxypeptidase into inactive fragments.^{5,6} It exhibits regulatory roles for plasma exudation, vascular permeability, nociception, and chronic inflammatory reactions.⁷⁻⁹ Moreover, bradykinin triggers cough reflex, induces bronchoconstriction, and increases airways resistance partly through the activation of bradykinin B₂ receptors.¹⁰ Bradykinin B₂ receptors have a high affinity for bradykinin. They are constitutively expressed on residential and immune cells in the airways,⁷ and inflammatory cytokines including tumor necrosis factor Alpha (TNF- α) and interleukin (IL)-1 β can up-regulate these receptors through activation of mitogen-activated protein kinase (MAPK) pathways.¹¹ Bradykinin may increase airways responsiveness to cationic peptide compounds¹² and its inhalation contracts bronchial smooth muscles in asthmatic patients.¹³ Based on pre-clinical findings, induction of airway constriction was inhibited by blocking bradykinin B₂ receptors (Hoe 140) in rat model.¹⁴ Compounds with ACE-

inhibitory effects compete with bradykinin for ACE binding sites, therefore, lower bradykinin degradation increases active bradykinin in the circulation and tissues¹⁵ causing angioedema and cough in ACE inhibitor-treated patients.^{5,16}

As experimental findings support, inactivation of bradykinin B₂ receptors by Icatibant (Trade name: Firazyr) reduces cough reflex induced by repeated ACE-inhibitor regimen.¹⁰ Cumulatively, these findings highlight the importance of ACE/bradykinin/bradykinin B₂ receptors pathway in bradykinin-mediated pulmonary effects that may have clinical importance in coronavirus pathophysiology and management.

It is noteworthy that the activity of the renin-angiotensin system as a modulator of vascular function is naturally high in the lungs. In this system, ACE converts angiotensin I (Ang I) to angiotensin II (Ang II) and produced Ang II, subsequently changes to Angiotensin 1-7 ([Ang 1-7]) under enzymatic activity of the ACE2.

The lungs express a high amount of ACE2 which may have a role in maintaining Ang II and Ang 1-7 balance.^{17,18} Ang II exerts vasoconstriction effects during hypoxic conditions and evokes pulmonary edema by increasing vascular permeability.¹⁹ Given this, increasing levels of Ang II may be associated with lung injuries. Interestingly, it has been shown that coronavirus uses ACE2 as a fusion site to invade target cells.¹⁸ In our scenario (as illustrated in Figure 1), on the one hand, with the fusion of coronavirus to ACE2 and formation of coronavirus/ACE2 complex, this complex down-regulates or abolishes ACE2 function, therefore, results in excessive accumulation of Ang II (or makes a biochemical gradient in this direction), and on the other hand, increased concentration of Ang II may dissipate the enzymatic capacity of ACE which must be free to metabolize bradykinin into inactive fragments. This situation may tip the balance toward the excessive deposition of bradykinin and activation of bradykinin B₂ receptors signaling in the lungs and subsequent occurrence of pulmonary complications. Accordingly, we hypothesized that pharmacologic blockade of bradykinin B₂ receptors and/or inhibition of the enzymatic activity of kallikrein by molecules such as aprotinin/ecallantide may be

effective in impedance of a roller coaster phenomenon of ACE/ bradykinin/ bradykinin B₂ receptors pathway. Focusing on the enzymatic inactivation of bradykinin and measuring bradykinin levels especially in the target organs' tissue in coronavirus affected patients, may have advantages for designing better therapeutic strategies.²¹

During the eerie process of submission and rejection in different journals, two new drafts were published whose point of view, fortunately, coincided with ours and strengthened it. One is in the form of a preprint²² and the other from a nearby center.²³ Both of these papers intended to enlighten the almost skipped over role of the bradykinin system among so many other cytokines in SARS-CoV-2 pathogenesis.

All we are going to raise here has a strong hypothetical content which has not been converted into a trial due to the novelty of the situation. There are clinical features quite characteristic of the disease that we think are best explained by this activation of bradykinin model:

a) Dry cough: Notoriously ascribed to bradykinin as the most frequent side effect of ACE inhibitors (notably not angiotensin receptor blockers) due to a rise in the bradykinin activity.^{24,25}

- b) The clinical scenario of the disease accompanies a prolonged course of dry cough lasting days to a few weeks and sudden aggravation of respiratory function leading to respiratory failure. We think this may be the result of aminopeptidase as an alternative catalyst of bradykinin running out of its capacity.²⁶ Aminopeptidase is a micro mineral zinc-dependent enzyme with a limited reserve that significantly runs out at some point leading to the sudden aggravation of the situation, thus leaving the bradykinin system unabated.
- c) Interestingly and congruent with the latter, the ameliorating effects of zinc supplements have been proposed.²¹
- d) An aggravating effect of ACE inhibitors on the disease is consistent with the role we are assigning to the ACE and its failure in bradykinin catalysis. At the same time, angiotensin receptor blockers are gradually moving to the safe side which may paradoxically even exert an enhancing effect on ACE after their chronic use.^{27,28}
- e) An early drop in O₂ saturation, bronchospasm, and increased vessel wall permeability is compatible with bradykinin activity.

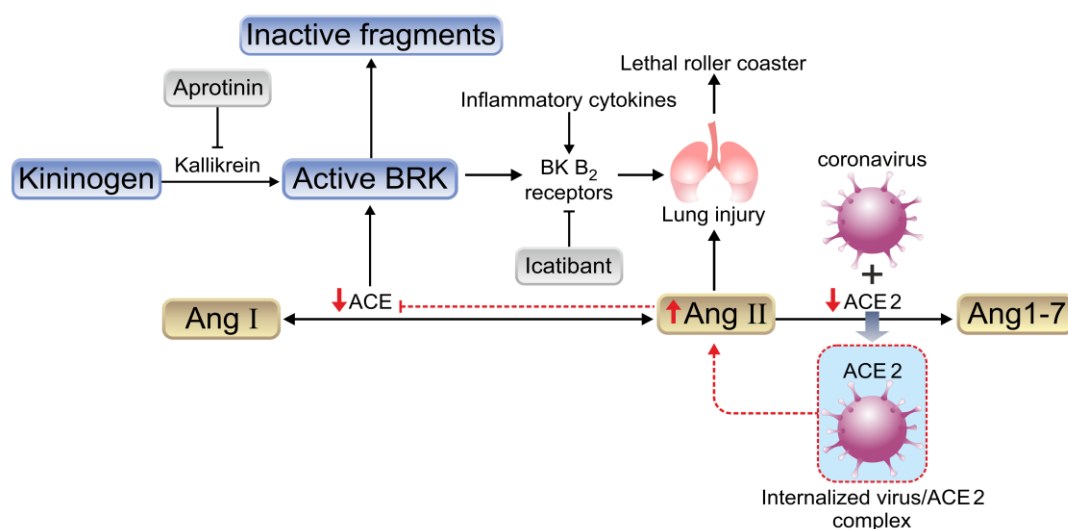


Figure 1. Schematic representation of involvement of angiotensin-converting enzyme (ACE)/ bradykinin/ bradykinin B₂ receptors pathway in coronavirus respiratory insult

Among smooth muscle relaxing factors, bradykinin is well known for its paradoxical action of causing bronchospasm. Under normal conditions, ACE converts Ang I to Ang II and inactivates bradykinin (BRK). In this pathway, ACE2 converts Ang II to Ang 1-7, hence reduces levels of Ang II and increases Ang 1-7 levels. Once coronavirus fused to ACE2, as its entry point, it forms virus/ACE2 complex, downregulates ACE2 surface expression, and results in internalization of virus/ACE2 complex. This increases the levels of Ang II and consequent damages of lung tissues. Also, increased levels of Ang II or the biochemical gradient may impact on the ACE capacity to such extent that it is unable to inactivate bradykinin competently. In the pulmonary system, bradykinin binds to BK B₂ receptors (which are expressed constitutively and under stimulatory effects of inflammatory cytokines) to induce bronchial contraction, vascular permeability, and inflammatory reactions and consequently these events together with deleterious effects of Ang II may worsen conditions in patients. In this scenario, the application of BK B₂ receptors antagonists (Icatibant) and/or inhibition of bradykinin synthesis by aprotinin/ecallantide may benefit patients.

In conclusion, due to the strong correlation of clinical findings with this hypothesis, designing clinical trials based on molecules including (but not limited to) Icatibant and Aprotinin or ecallantide may have priority over diverse therapeutic strategies.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-6.
2. Parker E. Covid 2019 tracker. 2020.
3. Shah SGS, Farrow A. A commentary on "World Health Organization declares global emergency: A review of the 2019 novel Coronavirus (COVID-19)". *Int J Surg*. 2020;76:128-9.
4. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-4.
5. Mukae S, Itoh S, Aoki S, Iwata T, Nishio K, Sato R, et al. Association of polymorphisms of the renin-angiotensin system and bradykinin B₂ receptor with ACE-inhibitor-related cough. *J Hum Hypertens*. 2002;16(12):857-63.
6. Sharma J. Activation of the bradykinin system by angiotensin-converting enzyme inhibitors. *Eur J Inflamm*. 2010.
7. Hewitt MM, Adams G, Jr., Mazzone SB, Mori N, Yu L, Canning BJ. Pharmacology of Bradykinin-Evoked Coughing in Guinea Pigs. *J Pharmacol Exp Ther*. 2016;357(3):620-8.
8. Ricciardolo FLM, Folkerts G, Folino A, Mognetti B. Bradykinin in asthma: Modulation of airway inflammation and remodelling. *Eur J Pharmacol*. 2018;827:181-8.
9. Takei Y, Ando H, Tsutsui K. Handbook of hormones: comparative endocrinology for basic and clinical research: Academic Press; 2015.
10. Fox AJ, Laloo UG, Belvisi MG, Bernareggi M, Chung KF, Barnes PJ. Bradykinin-evoked sensitization of airway sensory nerves: a mechanism for ACE-inhibitor cough. *Nat med*. 1996;2(7):814-7.
11. Zhang Y, Adner M, Cardell LO. IL-1 β -induced transcriptional up-regulation of bradykinin B₁ and B₂ receptors in murine airways. *Am J Respir Cell Mol Biol*. 2007;36(6):697-705.
12. Coyle AJ, Ackerman SJ, Burch R, Proud D, Irvin CG. Human eosinophil-granule major basic protein and synthetic polycations induce airway hyperresponsiveness in vivo dependent on bradykinin generation. *J Clin Invest*. 1995;95(4):1735-40.
13. Fuller RW, Dixon CM, Cuss FM, Barnes PJ. Bradykinin-induced bronchoconstriction in humans. Mode of action. *Am Rev Respir Dis*. 1987;135(1):176-80.
14. Homma T, Irvin CG. Bradykinin-induced bronchospasm in the rat in vivo: a role for nitric oxide modulation. *Eur Respir J*. 1999;13(2):313-20.

15. Taddei S, Bortolotto L. Unraveling the Pivotal Role of Bradykinin in ACE Inhibitor Activity. *Am J Cardiovasc Drugs*. 2016;16(5):309-21.
16. Kaufman MB. ACE Inhibitor-Related Angioedema: Are Your Patients at Risk? *P T*. 2013;38(3):170-2.
17. Kaplan AP, Joseph K, Silverberg M. Pathways for bradykinin formation and inflammatory disease. *J Allergy Clin Immunol*. 2002;109(2):195-209.
18. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450-4.
19. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. *Int J Pept*. 2012;2012:256294.
20. Wong MK. Angiotensin converting enzymes. *Handbook of Hormones: Elsevier*; 2016. p. 263-e29D-4.
21. Te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn²⁺ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS pathogens*. 2010;6(11).
22. van de Veerdonk F, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Bruggemann RJ, et al. Kinins and Cytokines in COVID-19: A Comprehensive Pathophysiological Approach. 2020.
23. Tolouian R, Vahed SZ, Ghiyasvand S, Tolouian A, Ardalani M. COVID-19 interactions with angiotensin-converting enzyme 2 (ACE2) and the kinin system; looking at a potential treatment. *Journal of Renal Injury Prevention*. 2020;9(2).
24. Andrejak M, Andrejak M-T, Osterman G. Enalapril, captopril, and cough. *Arch Intern Med* 1988;148(1):249-.
25. Overlack A. ACE inhibitor-induced cough and bronchospasm. *Drug saf*. 1996;15(1):72-8.
26. Guimarães JA, Borges DR, Prado ES, Prado J. Kinin-converting aminopeptidase from human serum. *Biochem Pharmacol*. 1973;22(24):3157-72.
27. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? *JAMA*. 2020.
28. Danser AHJ, Epstein M, Battle D. Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. *Hypertension*. 2020.