



Hypothesis: Bradykinin Blockers Might Reduce the Need for Ventilators for COVID-19 Patients

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Short Communication

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ABSTRACT

The symptoms of COVID-19, leading to pulmonary edema and the need for ventilators may be due to the fact that the virus increases bradykinin levels. If true, administering bradykinin blockers can provide a cheap way to reduce the severity of the symptoms and the burden on hospital resources, and, ultimately, the fatality rate.

Keywords: ACEIs; positive feedback; pulmonary edema.

1. INTRODUCTION

Hospitals are facing significant difficulties in response to COVID-19. One important challenge is due to the increasing need for ventilators, which stresses and has overwhelmed the current capacity of many hospitals. This paper puts forth a hypothesis regarding the underlining pathological mechanism that leads to the need for ventilators, and shows that it might be

possible to substantially reduce the need for ventilators by means of administering a bradykinin blocker to patients.

COVID-19 principal morbidity is due to pulmonary edema which inhibits oxygen perfusion [1]. This leads to low oxygen levels, drowning sensation, and panic. The present communication discusses the role of bradykinin, and a possible solution.

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2. DISCUSSION

ACE inhibitors (ACEIs) are believed to increase susceptibility to COVID-19 infection as a result of sharing similar receptors [2]. Diaz notes that “patients treated with ACEIs and [angiotensin receptor blockers] ARBS will have increased numbers of ACE2 receptors in their lungs for coronavirus S proteins to bind to” and, as a result, “they may be at increased risk of severe disease outcomes” [2]. This may be the consequence of a positive feedback, with ACEIs causing the up-regulation of receptors, similar to the effects that decreased exposure to agonists have on muscle acetylcholine receptors [3].

However, the bradykinin increasing properties of ACEIs may be to blame for the increased morbidity. Bradykinin is a well-known stimulator of vessel permeability and leakage mediated by its stimulation of the vasodilation-inflammation pathway [4,5], and a potent bronchoconstrictor of human airways [6]. There is strong evidence that

high bradykinin levels increase the risk of angioedema related to ACE inhibitors, which is resistant to antihistamines [7]. Previous research on bradykinin blockers in pulmonary edema (PE) in a non-COVID-19 context has shown that, indeed, “bradykinin aggravates adrenaline-induced PE through activation of the B2 receptor by the kallikreins although the precise mechanism is not known” [8]. Moreover, an expert meeting on angioedema has issued a number of recommendations specifically on how to diagnose and treat bradykinin-mediated angioedema [9].

Furthermore, the use of ibuprofen as a pain reliever has been associated with increased morbidity in people infected with COVID-19 [10]. Ibuprofen inhibits prostaglandins, diminishing the negative feedback on bradykinin production. This leads to a surge in bradykinin and its histamine pathway, further reducing oxygen perfusion in the lungs, and leading to a worsening of the symptoms (Fig. 1).

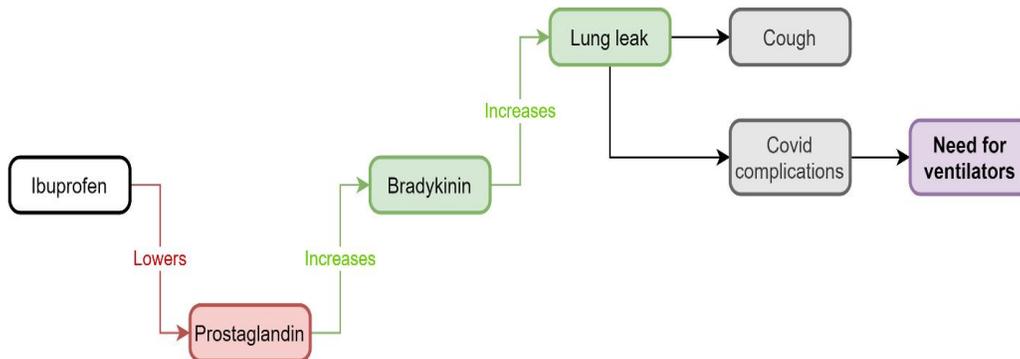


Fig. 1. Why ibuprofen makes things worse

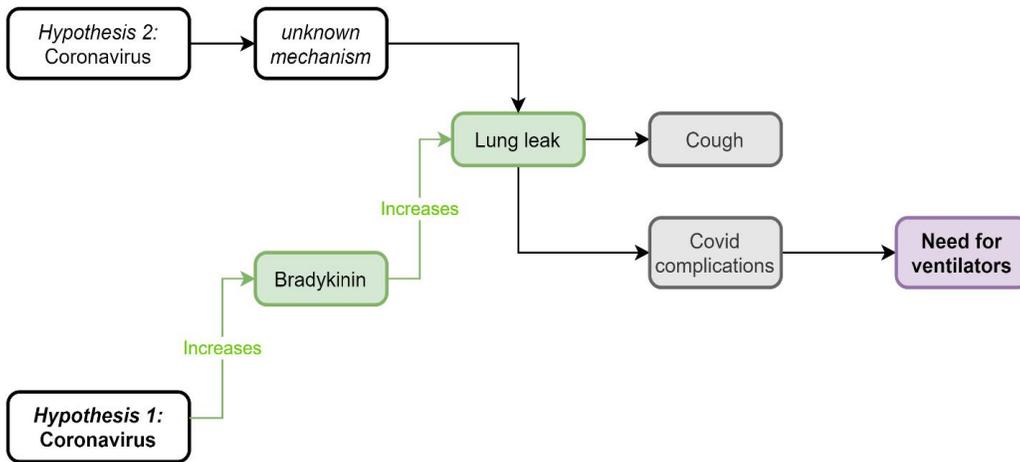


Fig. 2. Possible mechanisms by which the corona virus operates

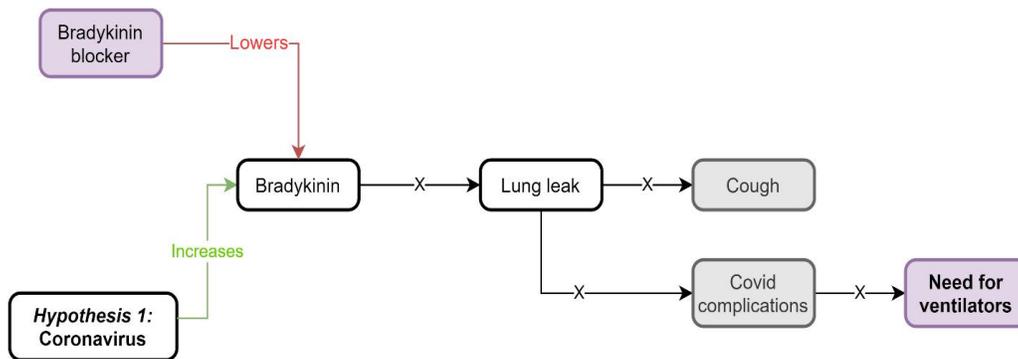


Fig. 3. Proposed remedy if hypothesis 1 is correct

We don't yet fully understand the mechanism by which COVID-19 infection leads to lung leak and the complications requiring ventilators (Fig. 2). A likely possibility, suggested by the ibuprofen effect and also evidenced by Folkerts et al. [11], is that the main cause for pulmonary edema seen in COVID-19 patients is the potentiated effect of bradykinin due to the viral infection. This is hypothesis 1 in Fig. 2.

If hypothesis 1 is true, administering a bradykinin blocker to patients may reduce pulmonary edema and airway hyperresponsiveness and, hence, the need for ventilators (Fig. 3). By contrast, if some version of hypothesis 2 in Fig. 2 is correct, bradykinin blockers would not lead to the same beneficial effects. Additional empirical research is needed to see if the mechanism by which COVID-19 operates is indeed that described by hypothesis 1. If so, we may have a cheap way to reduce the severity of the symptoms, patient morbidity and mortality, and the burden on hospital resources.

3. CONCLUSION

Several different lines of evidence point to the increase in bradykinin levels as a likely key mechanism by which the new coronavirus is causing lung leak, and, hence, leads to complications and a need for ventilators. If this is indeed the case, an easy and cheap solution is available: Administer a bradykinin blocker to patients. This should limit complications and the need for ventilators, thus allowing hospitals to care for a larger number of patients without having their resources overwhelmed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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