

High-dose ACEi might be harmful in COVID-19 patients with serious respiratory distress syndrome by leading to excessive bradykinin receptor activation

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ABSTRACT

Purpose: We aimed to critically review the available information on the potential contribution of excessive kallikrein-kinin systems (KKSs) activation to severe respiratory inflammation in SARS-CoV-2 infection, and the likely consequence of ACE inhibition in seriously affected patients. *Methods:* The literature related to the above topic was reviewed including papers that analysed the connections, actions, interactions, consequences and occasionally suggestions for rational interventions. *Results/Conclusion:* Severe broncho-alveolar inflammation seems to be caused, at least in part, by upregulation of the KKS that increases plasma and/or local tissue concentrations of bradykinin (BK) in patients with COVID-19 infection. Besides KKS activation, suppression of ACE activity results in decreased bradykinin degradation, and these changes in concert can lead to excessive BK B1 and B2 receptor (BKB1R/BKB2R) activation. Aminopeptidase P (APP), and carboxypeptidase N also degrade bradykinin, but their protein expression and activity are unclear in COVID-19 infection. On the other hand, ACE2 expression is upregulated in patients with COVID-19 infection, so ACE2 activity is unlikely to be decreased despite blockade of part of ACE2 by the virus for

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entry into the cells. ACE2 cleaves lys-des-arginine⁹BK and arg-des-arginine⁹BK, the active metabolites of bradykinin, which stimulate the BKB1R receptor. Stimulation of BKB1R/BKB2R can exacerbate the pulmonary inflammatory response by causing vascular leakage and edema, vasodilation, smooth muscle spasm and stimulation of pain afferent nerves. Despite all uncertainties, it seems rational to treat comorbid COVID patients with serious respiratory distress syndrome with ARBs instead of high-dose ACE inhibitor (ACEi) that will further decrease bradykinin degradation and enhance BKB1R/BKB2R activation, but ACEi may not be contraindicated in patients with mild pulmonary symptoms.

KEYWORDS

COVID-19, cardiovascular, respiratory inflammation, RAS, ACE2, kallikrein-kinin system, bradykinin, ACE-inhibitor, angiotensin receptor blocker, old patient, hypertension

INTRODUCTION

The high mortality rate of elderly vulnerable hypertensive patients infected with acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is often associated with cytokine storm [1]. Several cytokines were measured or suggested to contribute to the development of serious pulmonary inflammation [2–4] but no direct information is available on the plasma or tissue concentrations of bradykinin and kallidin (lysine-bradykinin), and their active metabolites (bradykinin-related peptides). The kallikrein-kinin system (KKS) is upregulated in many inflammatory diseases [5], and in the bronchoalveolar lavage fluid of COVID-19 patients [6]. Therefore, it seems reasonable to assume that the concentration of bradykinin peptides is markedly elevated in COVID-19 patients. The consequent overactivation of bradykinin B1 and B2 receptors (BKB1R/BKB2R) prompted us to ask the question: is angiotensin converting enzyme (ACE) inhibitor treatment safe in patients with virus-induced severe pulmonary inflammation? (Fig. 1)

THE KALLIKREIN-KININ SYSTEM

The KKS, an endogenous multiprotein cascade, has a basic physiological/pathophysiological role not only in the coagulation pathway (risk of thrombosis) but also in the inflammatory response via bradykinin and bradykinin-related peptides. There are 15 tissue kallikrein proteins, out of which kallikrein 1 is the main type expressed in the lung tissue of healthy persons. However, all 15 kallikreins are robustly expressed in COVID-19 patients. The bradykinin-related peptides cleaved from kininogens have a variety of actions including vasodilatory activity, increased vascular permeability and nitric oxide production, spasm of smooth muscle in airways, exaggerated release of several cytokines by leukocytes and of prostaglandins and leukotrienes by various cell types [7, 8]. The short bradykinin B2 receptor (B2) is constitutively expressed and stimulated mainly by bradykinin, and it is mainly involved in the early inflammatory reactions by causing vasodilation, smooth muscle contraction and by releasing arachidonate products and pro-inflammatory cytokines. Arachidonic acid release temporarily desensitises the B2 receptor, which is, however, rapidly re-sensitised by several factors, including angiotensin 1-9 and bradykinin [9, 10]. The actions of active bradykinin-metabolites, such as des-arginine⁹BK (DABK)



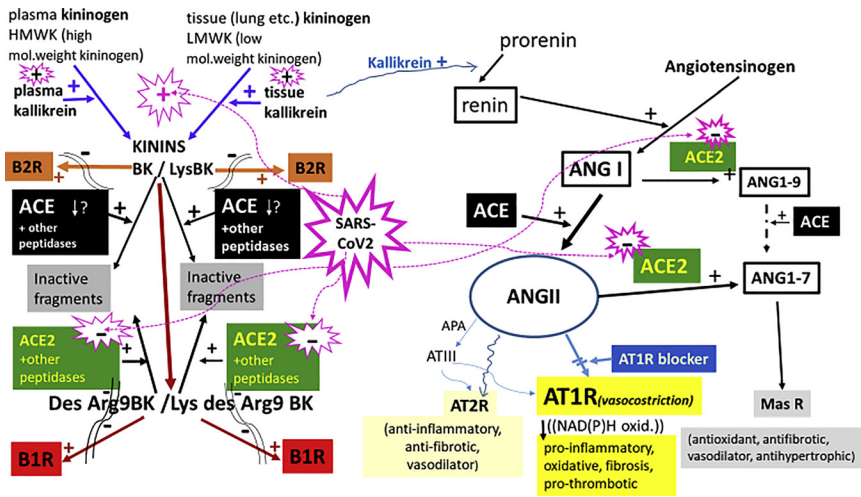


Fig. 1. Relationship of RAS and kinin-kallikrein system and its changes in SARS-CoV-2 infection based on Veerdonk et al. [6].

Abbreviations: ANGI, ANGII: angiotensin I, angiotensin II; APA: aminopeptidase-A; AT1R: angiotensin II type 1 receptor; AT2R: angiotensin II type 2 receptor; ATIII: angiotensin III; B1R: bradykinin type 1 receptor; B2R: bradykinin type 2 receptor; Des Arg9BK: [des-Arg⁹]-bradykinin; Lys desArg⁹ BK: [Lys-des-Arg⁹]-bradykinin; NAD(P)H oxide: NAD(P)H oxidase. MAS: mitochondrial assembly receptor (PCR (G-protein-coupled receptor), through which Ang (angiotensin)-(1-7) signals

and lys-des-arginine9BK (LYDABK) are mediated via BKB1R, which is induced by tissue injury and pro-inflammatory cytokines. BKB1R initiates an array of long-lasting intracellular and intercellular responses, including increased vascular permeability and release of a variety of biologically active pro-inflammatory agents [11, 12]. Therefore, in COVID-19 infection both BKB2R and BKB1R play a significant and complex role in severe pulmonary and multi-organ inflammation. Their signal transduction can even be enhanced by spontaneous BKB2R–BKB1R-complex formation [13]. The KKS has multiple interactions with other endogenous metabolic cascades, such as the renin-angiotensin system (RAS) and the complement system [14, 15]. SARS-Cov-2 activates the KKS axis in the bronchoalveolar tissue [16]. Although there are some uncertainties, the upregulated kallikrein is likely able to modulate the RAS by increasing prorenin expression [17]. On the other hand, both ACE and ACE2, the two major intrinsic regulators of RAS, have an inhibitory effect on KKS by their strong and specific kininase activity [11, 18]. Imai et al. stressed the significance of this relationship already in 2007 in acute respiratory distress syndrome (ARDS) [19]. Downregulation of ACE2 expression by HCoV-NL63 coronavirus was also proved (but some opposite results are also available) during that period [20, 21]. However, ACE2 mRNA expression was strongly induced in the bronchoalveolar lavage fluid of COVID-19 patients [16]. Based on the assumption that ACE2 activity is decreased by its occupation by the virus, and, consequently, decreased destruction of the inflammatory mediator des-arg9-bradykinin and consequent BKB1R activation can lead to worse disease outcome, it was suggested that blocking BKB2R and inhibiting plasma kallikrein activity can be beneficial [6]. Another problem is, whether or not the supposedly higher ACE2 expression induced by



ACE inhibitor therapy promotes the dynamics of SARS-CoV-2 entering into respiratory tissues [22]. Thus, considering the relationship between severe respiratory inflammation and RAS inhibitor therapy, the majority of publications focused mainly on „bad” ACE2 as the receptor for SARS CoV-2 and „good” ACE2 promoting the conversion of the vasopressor and pro-inflammatory angiotensin II to vasodilator and anti-inflammatory angiotensin 1-7 [23]. The recommendation of papers and scientific societies was not to stop or change cardiovascular ACE inhibitor therapy after the start of infection in SARS-CoV-2 patients [24], although expression of ACE is increased and ACE2 is decreased in old, vulnerable patients that leads to higher AngII and lower Ang(1-7) concentrations and an unfavourable balance between AT1R and Mas receptor (MasR) activation [25]. One pillar of this initiative was that following SARS-CoV-2 infection, the vasoconstrictor and pro-inflammatory angiotensin II level was elevated [26], but it was assayed using a method criticised later [27]. However, these authors neglect the role of the closely related KKS.

The above-cited scientific knowledge on the KKS and the role of bradykinin as an important player that can directly affect the clinical outcome in severe respiratory and systemic inflammation and can contribute to the cytokine storm was mentioned in several papers [1, 6, 14, 28–30]. On the basis of earlier scientific findings, some researchers tried to prove the pathological importance of KKS in the inflammatory process by combined BKB1R and BKB2R blockade or kallikrein inhibition, assuming increased BK and DABK/LYDABK concentrations and higher BKB1R and BKB2R receptor activation in COVID-19 infection although no approved inhibitors are available [6, 15]. Some of these interventions improved pulmonary inflammation in experimental animals, supporting a role of KKS and BK in severe respiratory and systemic inflammation caused by SARS-CoV-2 infection [6, 15]. Replacing kininase activity of ACE2 (neprilysin) may offer partial therapeutic promises for severe COVID-19 patients in the future [6, 30]. Another potential way to inhibit BKB1R activity is blocking innate cytokines (IL-1) that upregulates BKB1R on endothelial cells at the site of inflammation [6].

RAS DYSREGULATION

RAS dysregulation and dysregulated RAS-KKS interaction can have an important role in severe COVID-19 inflammation. Potential virus-induced kallikrein-prorenin upregulation was already mentioned above. The basic intrinsic regulator ACE2 enzyme/ACE2-receptor system appears to be Janus-faced in coronavirus infection [23]. The ACE2-receptor is the cellular entry point (spike protein) for coronaviruses that leads to severe inflammation in the lungs or in other organs [19, 23]. This could mean that increased expression of the ACE2 gene may accelerate SARS-Cov-2 replication. Moreover, it has been also described that bradykinin, angiotensin and coagulation system proteins are co-expressed with ACE2 in alveolar cells [31]. This relationship provoked much debate on the potential danger of ACE inhibitor treatment-induced ACE2 upregulation. However, this upregulation was supported by findings from animal experiments, but clinical studies or observations could not prove it [32].

There are contradicting results whether ACE 2 expression was downregulated or upregulated after binding of the virus spike protein to the ACE2 receptor [33]. Previous experiments with other coronaviruses mostly found downregulation [20]. It should be noted that increased expression of ACE2 does not mean higher peptidase activity in COVID-19, because the ACE2



protein will likely be used for viral entry, i.e. invasion of host cells, and not for peptidase activity. A recent observation further complicates the issue, as binding of the spike protein to ACE2 increased peptidase activity, *in vitro* [34]. However, the clinical consequence and time-course of this finding is unclear, as the SARS-CoV-2-ACE2 complex is internalised shortly after binding.

After interaction with the viral spike protein, ACE2 is internalised along with the virus and the spike protein is proteolytically cleaved by type II transmembrane serine protease (TMPRSS2). The metalloproteinase domain 17 (ADAM17) and TMPRSS2 upregulation (activated partly by decreased ACE2 activity that increases Ang II concentration and AT1 receptor activation) leads to proteolytic cleavage of the ACE2 ectodomain, shedding it into the extracellular space. ADAM17 also cleaves TNF α , IL-6 and other proinflammatory molecules releasing them from the cell membrane [33]. The complexity of these events in COVID-19 can explain that the level of ACE2 in plasma measured by immunoassays can hardly inform us about the real (and changing) rate of expression and activity of membrane-bound ACE2 [20]. In the 'post-infection' phase ACE2 activity can probably provide some anti-inflammatory effects. Theoretically, the RAS inhibitor-induced ACE2 upregulation could be useful in this phase, if this effect exists at all. The anti-inflammatory activity of ACE2 and its relation to bradykinin activity has been first proven in a 'virus-free' experiment: the experimentally reduced ACE2 activity resulted in both increased activity of the BKB1R axis and the exacerbation of artificially induced inflammation in a cell culture [35]. One of the ACE2-induced potentially protective, anti-inflammatory mechanisms is that ACE2 can convert the vasoconstrictor and weak pro-inflammatory peptide Ang II to angiotensin 1-7, which in turn has some anti-inflammatory effect via MasR. Another protective, probably more important effect in COVID-19 is that ACE2 is also a kininase for DABK and LYDABK. Therefore, ACE2 can reduce the activation of the strong inflammatory mediator BKB1R and inhibit broncho-alveolar inflammation [19, 35]. The inter-individual and ethnic variability of infectivity and the clinical outcome of Covid-19 pneumonia can most likely be explained by the various levels of ACE2 activity before and/or after the entry of coronavirus via ACE2 into the bronchoalveolar cells. In this respect it is interesting that the individual expression rate and pattern of ACE2 gen (genetic variants of ACE2 with different affinities for spike protein) seem to depend on gender, age and perhaps ethnic factors (higher in women, lower in elderly and higher in East Asians) [5]. However, very recent publications highlighted contradictions and methodological problems in some studies, and drew attention to the need of reinvestigation using extended and up-to-date methodology [36]. If the similarly questionable validity of the suggested ACE2 upregulation by RAS inhibitor-treatment could be conclusively demonstrated, it would also support the anti-inflammatory usefulness of this intervention in the post-infection period [37]. The previously proposed ACE upregulation [38] has not been proven recently in essentially hypertensive patients with or without COVID-19 infection [16]. Similarly, no higher Ang II levels were found in their plasma, when really valid and sensitive assays were carried out [27]. ACE as a kininase also cleaves the bradykinin peptide. Inhibition of this ACE-related kininase activity results in the well-known side effects (cough, angioneurotic oedema) [6, 18, 29]. When a higher dose of ACEi is used, it results in a supra-normal level of bradykinin concentration in the bronchoalveolar tissue. This bradykinin excess-related irritative and inflammatory effect of ACE inhibitors can become more dangerous in COVID-19, as it adds on to the already markedly increased bradykinin level. Several pathological mechanisms in KKS-RAS inter-regulation can promote the development of the SARS-CoV-2 related inflammation, resulting in increased production and suppressed degradation of



bradykinin and its active metabolites leading to highly activated BKB2R and DABK/LYDA BKB1R axes. The former possibility is based on the 'Veerdonk model', i.e. suppressed ACE2 expression and activity, similarly to the earlier coronavirus infections [6], and the latter is based on the model described by Garwin et al., i.e. lower ACE and enhanced ACE2 expression, but unknown ACE2 activity because of its fusion with coronavirus and cellular internalisation, and overexpression of BKB2R and BKB1R [16]. The most important arguments for a major role of RAS imbalance and KKS activation in unfavourable outcome in seriously infected patients are the following:

- a) The SARS-COV-2 virus can directly increase bradykinin production by kallikrein (and kallidin) upregulation [16].
- b) Binding of the virus spike protein to ACE2 uses up ACE2 and, consequently, decreases the cleaving of DABK and LYSDABK and increases BKB1R activation.
- c) In the case of lower ACE activity, Ang(1-9) (produced by ACE2 from angiotensin I in small amounts) is less converted to Ang(1-7) peptide, so it may facilitate BKB2R resensitisation [16]. Spontaneous BKB2R–BKB1R-complex formation may further increase BKB1R activation [11].
- d) A recent study from Garwin et al. highlighted the outstanding significance of not only the critically increased bradykinin axis (thousand-fold and hundred-fold upregulation of BKB1R and BKB2R mRNA, respectively), but also the surprisingly strong, 8-fold downregulation of ACE mRNA expression in bronchoalveolar lavage fluid (BALF) from COVID-19 patients [16]. The affinity of ACE is higher for the degradation of bradykinin than for Ang I-Ang II conversion [39]. Therefore, in this special pathological situation inhibition of ACE activity means rather less bradykinin cleaving, and, as a consequence, a critically dangerous activation of BKB2R and BKB1R [13, 16].

CONCLUSIONS

In severe COVID-19 pulmonary infection the excess of bradykinin and its active metabolites and the consequent BKB2R and BKB1R hyperactivation might play an important role in the development of critical bronchoalveolar inflammation and ARDS (bradykinin-cytokine storm).

The background of this pathological condition includes an increased production of bradykinin due to virus-induced kallikrein-kinin upregulation, dysregulated RAS-KKS relationship, consequently decreased kininase activity, insufficient degradation of BK, DABK and LYDABK, extremely high BKB2R and BKB1R (inducible) expression.

In this state, the inhibition of the already downregulated ACE activity may result in bradykinin-related critical worsening of the hyperinflammation in the lungs.

Switching from high dose ACEi to ARB or to other antihypertensive drugs in the most severe cases of RDS may help avoid ACEi-triggered harmful pharmacological enhancement of the severe bronchoalveolar BK-related hyperinflammation. In fact, a recent study aimed to inhibit kallikrein by aprotinin, a competitive inhibitor of several serine proteases, in combination with low molecular weight heparins, as it was suspected that the KKS-BK overactivation played a major role in the thrombotic and inflammatory responses in COVID infection [40]. However, in less severe cases ACEi is not contraindicated as shown recently [24, 41]. Therefore, our



suggestion to avoid ACEi is restricted to the most severe SARS-Cov-19 infected, ARDS cases with life-threatening virus-activated cytokine storm.

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