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The COVID-19 outbreak and the angiotensin-converting enzyme 2: too little or too much?

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The current outbreak of coronavirus disease 2019 (COVID-19) constitutes a major challenge for the world's medical systems. None of the available antiviral drugs has proven efficacy in controlling this viral disease. The mortality rate is especially high in patients with risk factors, e.g. older age, male gender, cardiovascular comorbidities, high blood pressure and diabetes.

The fact that the cell receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is angiotensin-converting enzyme 2 (ACE2) [1] has raised questions about the relationship between the renin–angiotensin system (RAS) and the severity of COVID-19. It has been suggested that the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) by patients with high blood pressure, diabetes or cardiovascular comorbidities increases the risk of COVID-19 because both of these drug class are known to upregulate ACE2 expression [2]. The elevated level of pulmonary ACE2 might facilitate viral entry into pneumocytes and thus pave the way for acute respiratory distress syndrome (ARDS, the main cause of death in COVID-19). Consequently, some experts have suggested that withdrawal of ACEIs/ARBs in these high-risk patients might reduce the likelihood of severe lung disease [3].

However, a careful review of the literature prompted us to consider the opposite point of view with regard to the interaction between the RAS and the severity of COVID-19.

In fact, several studies have shown that SARS-CoV, H7N9 influenza and respiratory syncytial virus infections are associated with a progressive depletion of pulmonary ACE2 [4–6]. Might this depletion be instrumental in the genesis of lung damage? Indeed, it has been shown that the RAS system in the lung is involved in ARDS, with an increase in ACE1 levels in the patients' bronchoalveolar lavage fluid [7]. Moreover, there is an association between the D/D ACE1 genotype [associated with high levels of ACE and angiotensin (Ang) II] and the severity of ARDS' [8]. The interaction between AngII and its type 1 receptor leads to pulmonary inflammation and capillary leakage, both of which contribute to the initiation and/or the aggravation of ARDS. It is noteworthy that an elevated plasma concentration of AngII has been observed in H7N9 virus patients with ARDS with an unfavourable course, but not in those with a favourable course [5]. Besides its role in ARDS, the RAS has also been involved in other lung pathologies such as chronic obstructive pulmonary disease and pulmonary hypertension or lung cancer. *ACE* polymorphism might contribute to the risk of chronic obstructive pulmonary disease and pulmonary hypertension in Asian patients [9], and high-altitude pulmonary oedema [10].

ACE2 degrades AngII to Ang(1–7); the latter is known to have a counter-regulatory role in the RAS. This beneficial action is observed throughout the cardiovascular system and in the kidney [11]. The beneficial effects of ARB therapy may partially result from an increase in ACE2 expression and from the formation of Ang(1–7).

It has been shown that patients with ARDS caused by various infections have low lung levels of ACE2 [12]. In several animal models, the administration of recombinant ACE2 reduced inflammation and lung damage, and increased oxygenation [12–14]. Furthermore, the administration of Ang(1–7) in these models led to similar anti-inflammatory effects [15]. ACE2 could also mitigate pulmonary inflammation through its catabolism of [des-Arg9]-bradykinin, the active metabolite of bradykinin. Through its activation of the bradykinin1 receptor and the secretion of chemokines such as CXCL5, [des-Arg9]-bradykinin has been shown to be involved in the genesis of pulmonary inflammation observed after endotoxin inhalation [16].

Through its link to ACE2 internalization, SARS-CoV-2 might exhaust pulmonary ACE2, and thus induce a counter-regulatory system that opens the way to the harmful inflammatory effects of AngII in the lung. The progressive exhaustion of pulmonary ACE2 might explain the two disease phases often observed in COVID-19 patients, i.e. an abrupt aggravation after an initial week of mild-to-moderate lung symptoms.

Patients with COVID-19 often suffer from comorbidities like acute kidney injury, myocardial injury and neurologic symptoms; given the effects of ACE2 depletion on these organs, these comorbidities might also be linked to the decrease in ACE2 expression [11].

In rats, the pulmonary ACE2 level falls with age [17]. Again, rapid exhaustion of pulmonary ACE2 might explain why older adults are most at risk of severe COVID-19. Likewise, there are some reports of low ACE2 activity in obesity-induced hypertension in males [18] and in diabetes [19], which might also explain the greater potential risk observed in patients with these comorbidities.

Many studies of the cardiovascular or renal systems in rats treated with ARBs (e.g. losartan and olmesartan) have demonstrated that these drugs are associated with elevated expression of ACE2 [2] and thus elevated levels of Ang(1–7); the latter has anti-inflammatory and anti-fibrotic effects through its own receptor (MAS G protein-coupled receptor) [11]. It has been demonstrated more specifically in mouse models of ARDS that losartan and Ang(1–7) decrease lung injury and fibrosis [12, 15]. The time course of the effect of ARBs on ACE2 seems to be in line with its potential use in clinical trials. Indeed, in mice models of ARDS, losartan was injected just 30 min before the induction of ARDS, a sufficient time to protect against the development of ARDS [4, 13, 20]. ACEi might also be protective, since captopril was demonstrated to decrease lung lesions in a chemical rat model of ARDS [21].

In view of the above, we suggest that ACEi/ARBs treatment could be maintained in order to prevent the decrease in pulmonary ACE2 levels. We acknowledge that the balance between ACE2 facilitated viral entry into pneumocytes and the beneficial effects of increasing the expression and the activities of ACE2 remain unexplored. Moreover, the clinical effects of this ACE2-directed approach are complex and may depend on the ACE1/ACE2 imbalance at the onset of ARDS. This imbalance depends on the ACE1 genotype (D/D versus D/I or I/I), the presence of other pathologies, the use of drugs influencing the RAS and/or the extent of ACE2 depletion by the virus. We therefore suggest that the plasma AngII concentration could be a potential biomarker of profound ACE2 depletion and thus may identify individual patients who could develop a critical form of COVID-19 and benefit from treatment with an ARB.

SARS-CoV-2 is also suspected to directly affect glomerular and tubular cells through its entry via the ACE2 glomerular and tubular expression. Post-mortem histopathology of Chinese patients deceased from COVID-19 supports this hypothesis, with viral particles detected in glomerular and tubular cells by electronic microscopy or immunohistochemistry of viral proteins [22]. However, recent reports of kidney biopsies in non-deceased patients give different results. Indeed, Larsen *et al.* did not detect any viral particles by electron microscopy or immunohistochemistry in one woman with similar kidney lesions [23]. The role of ACE2 could also be more complex than expected in the pathophysiology of kidney lesions. Indeed, ACE2 deficiency exacerbates nephrin down-regulation and kidney inflammation in the ApoE-mutant mice while recombinant human ACE2 supplementation alleviates inflammation, renal dysfunction and glomerulus injury [24]. Thus, we cannot exclude that our strategy to increase ACE2 expression through ARBs could potentially decrease the risk of severe glomerular or tubular injury in COVID-19 patients.

In conclusion, we propose clinical trials in which the plasma AngII concentration will be monitored during the first few days of COVID-19, as a surrogate marker of pulmonary ACE2 activity. Depending on the AngII concentration results, the ARB treatment could be initiated in patients with high and continuously increasing plasma AngII concentrations. The use of AngII dosage to select people for whom the benefit of ARB will be maximal allows us to think that the risk of ARBs-induced acute kidney injury will be less with that approach as compared with a non-targeted approach with ARB treatment. The AngII-guided approach would allow balancing of the indication and the posology of treatment with ARBs.

CONFLICT OF INTEREST STATEMENT

None declared.

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