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Opinion

Are ACE inhibitors and ARBs more beneficial than harmful in the treatment of severe COVID-19 disease?

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After starting in China four months ago, the COVID-19 pandemic now affects most countries and has already caused more than 200,000 deaths by April 26, 2020

Under chest computerized tomography scans, the majority of severe COVID-19 patients show bilateral ground glass-like opacities and subsegmental areas of consolidation indicative of pneumonia. If in its severe forms this disease affects the lungs, in many cases it is also responsible for a multi-organ failure with adverse myocardial remodeling, myocardial stress, and cardiomyopathy [1,2]. The most distinctive comorbidities in patients who died from COVID-19 are hypertension, coronary heart diseases, cerebrovascular diseases and diabetes, and among them several were treated by Renin Angiotensin System (RAS) blockers, ACE inhibitors (ACEi) and AngII receptor blockers (ARBs) [3].

If we understand the pathophysiology of the disease a little better every day, there are still many gray areas regarding the intimate molecular mechanisms that make some people practically asymptomatic while others, in particular those with hypertension or cardiovascular diseases, rapidly progress to death. To try to better understand how SARS-CoV-2, the *Betacoronavirus* responsible for the COVID-19 disease, can cause deadly cardiovascular pathologies when it is supposed to infect the epithelial cells of the pulmonary alveoli, we must first return to the analysis of the virus tropism. The SARS-CoV-2 was found to bind to the human angiotensin I converting enzyme 2 (ACE2) cell surface monocarboxypeptidase [4]. ACE2 regulates the Renin-Angioten-Aldosterone System (RAAS), thus controlling blood pressure. Hence the question of whether RAS blockers should be maintained or stopped in the treatment of patients who, in addition to their cardiovascular pathologies, have contracted SARS-CoV2 [5]. By mid march 2020, the international professional societies of cardiology recommended continuing RAS blockers in SARS-CoV-2 positive patients [6].

What happens when the virus attaches to the ACE2 receptor is not yet fully known. To date, more information has been accumulated on SARS-CoV, a *Betacoronavirus* very similar to SARS-CoV-2 (which is also an ACE2-tropic virus), than SARS-CoV-2 itself. A recombinant SARS-CoV spike protein was found to down regulated the cell-surface expression of ACE2 through release of soluble ACE2 (sACE2) [7]. Similarly, the expression of ACE2 was found down regulated in cells infected by SARS-CoV [8]. However, it was also reported (in an article that has not been peer reviewed so far), that SARS-CoV up-regulate the expression of ACE2 in lung tissue thereby accelerating viral replication and spread [9]. For the moment it is not really known what happens in terms of expression of ACE2 in COVID-19 patients, in particular whether there is an increase or a decrease in the expression of the ACE2 receptors and whether these changes concern all cells or if these variations can be different among cell subpopulations. This is currently under investigation in our laboratory. In the literature it was already reported that reduced levels of cardiac ACE2 are associated with hypertension, dyslipidemia, and/or heart failure [10-12]. It remains also important to question whether or not ACE2 maintains its protease function when engaged in interaction with the SARS-CoV-2 spike. It can be speculated that when the SARS-CoV-2 spike binds to the ACE2 receptor in the a helix 1 and b5 region, it likely reduces the catalytic properties of ACE2 since these regions belong to the protease domain of ACE2. However this will be worth to be further explored.

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The main function of ACE2 is the regulation of blood pressure through the RAAS. ACE2 converts the octapeptide [Asp-Arg-Val-Tyr-Ile-His-Pro-Phe] angiotensin II (AngII) to the heptapeptide Ang(1-7) by hydrolysis of its C-terminal residue. By catalyzing this reaction, ACE2 limits the adverse vasoconstrictor and profibrotic effects of AngII [13], as well as the oxidative stress of AngII on endothelial cerebral arteries [14]. Ang (1-7) exerts its preventive effect through the MAS-related (MAS1) G protein-coupled receptor (GPGR) [15]. Disruption of ACE2 thus results in accumulation of AngII and cardiac dysfunction [16], because ACE2 no longer regulates the levels of vasoconstrictor AngII generated from the cleavage of the AngI decapeptide by a zinc metallopeptidases angiotensin converting enzymes (ACE) [17]. When overexpressed, AngII triggers cell signaling through binding to the seven-transmembrane receptor (7TM) angiotensin II type A receptor (AT_1R) [18]. Ang II also stimulates the release of various cytokines [19], which may be involved in the cytokine storm described in severe COVID-19 disease. It is therefore necessary to look at RAS blockers drugs, ACEi and ARBs (that targets the AT_1R), in the light of the most recent knowledge about the AngII and ACE2 regulations in the context of SARS-CoV-2 infection, before suggesting whether they are beneficial or harmful in this particular infectious disease. Although we cannot extrapolate data obtained on one cell type to another, it was reported that ACEi can increase ACE2 mRNA expression in the intestine [20]. The overexpression of ACE2 under ACEi treatment could increase the cleavage of AngII but could also promote the cellular uptake of SARS-CoV-2. To date it is still difficult to conclude whether this overexpression of ACE2 is, or is not, favorable to COVID-19 patients.

It can be hypothesized that by treating patients with ACEi this should reduce the accumulation of AngII by preventing ACE mediated cleavage of AngI. Furthermore, the fact of treating patients with ARBs, should prevent free AngII from inducing pro-inflammatory processes via the AT_1R receptors. Therefore, if the SARS-CoV-2 can directly or indirectly reduce the peptidase activity of ACE2, the use of RAS blockers should, in theory, be beneficial [21]. But, in this case, why do COVID-19 patients under RAS blockers therapy seem to be among the ones with the worst prognosis? There are certainly many parameters to consider, especially the age of patients which we know is a factor of poor prognosis. An early study form China reported that compared to COVID-19 survivors, non-survivors were older (64.6 years vs 51.9 years), more likely to develop SARS-CoV-2-related acute respiratory distress syndrome (ARDS; 81% patients vs 45% patients), and more likely received mechanical ventilation (94% patients vs 35% patients) [22]. Since, all world studies confirm that the risk for severe disease and death from COVID-19 is higher in older age groups with 80% of deaths occurring among adults aged ≥65 years and the highest percentage of severe outcomes being reported among persons aged ≥85 years [23,24]. Severe COVID-19 cases remain exceptional among persons aged ≤19 years while very many cases are reported among older adults living in long-term care facilities. Currently in the USA, 31% of cases, 45% of hospitalizations, 53% of intensive unit care (ICU) admissions, and 80% of deaths associated with COVID-19 were among adults aged ≥65 years. Moreover, elderly patients very often face hypertension problems.

Thereby, are RAS blockers harmful in the treatment of severe COVID-19 disease or does it highlights hypertension as a major factor of comorbidity in COVID-19 patients? To remove this uncertainty, it is now crucial to measure both the expression of ACE2 and AngII in COVID-19 patients with or without RAS blocker treatment. Such experiments are underway in our laboratory.

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Competing interests

CD declare a link of interest with the Sanofi and Merck pharmaceutical companies.

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