Speculation is not evidence: antihypertensive therapy and COVID-19

Giovanni de Simone and Costantino Mancusi

European Heart Journal - Cardiovascular Pharmacotherapy
doi:10.1093/ehjcvp/pvaa021

In 2003, a group of Chinese investigators documented that angiotensin-converting enzyme 2 (ACE2) is a functional receptor of the SARS-CoV virus.1 The virus–ACE2 receptor binding is thought to be responsible for cell invasion and ultimately for the manifestation of the disease.2 Right after the warning of a new SARS outbreak (COVID-19) related to a new coronavirus of bat origin, called SARS-CoV2, Chen et al.3 documented that the SARS-CoV2 receptor-binding domain
also exhibits strong interaction with ACE2, followed by evidence that, similarly to SARS-CoV, SARS-CoV2 uses the ACE2 receptor for cell entry.4 Similarly to the SARS-CoV virus, SARS-CoV2 is thought to down-regulate the ACE2 receptor,2 but does not affect ACE, thus substantially reducing the counter-regulatory effect of the ACE2 system and amplifying the effect of angiotensin II (AngII). ACE2 cleaves AngII and also angiotensin I (AngI),5 and generates a smaller peptide, angiotensin 1-7 (Ang1-7) regulating the availability of AngII at the AT1 receptor level. Ang1-7 binds a specific Mas receptor6 to counteract AngII activity with opposite effects,7 i.e. vasodilation, anti-inflammation, and antiproliferation. The down-regulation of ACE2, also due to SARS-CoV2 infection, therefore affects the regulation of the renin–angiotensin system (RAS), especially in the lung and kidney, but also in the heart, where ACE2 is well represented.8 Blunting the inhibitory regulation of ACE2 would leave AngII binding on the AT1 receptor free from an important counter-regulation, with consequent uncontrolled pro-inflammatory action and further down-regulation of ACE2 due to positive feedback with AngioII.9 In animal experiments, during SARS-CoV infection or recombinant SARS-CoV spike protein binding to ACE2, the

devastating inflammation of the lungs could be prevented by losartan, the ancestor of AT1 receptor blockers (ARBs).2 A review recently published clearly indicates the possibility of using ARBs as a therapy for COVID-19.4 Controlling AngII production with ACE inhibitors or ARBs breaks down the positive feedback reported for AngII and ACE29 and helps in restoring the ACE2 domain. The AngioI cleavage induced by ACE2 also produces another peptide, angiotensin 1-9 (Ang1-9),5 able to reverse experimental hypertension and thought to potentiate bradykinin action and to activate the counter-regulatory AT2 receptor.10 On 11 March, The Lancet. Respiratory Medicine published a letter by Fang et al.11 that is having great impact both in the conventional and social media, raising and spreading alarm among physicians and hypertensive
patients. The hypothesis of the authors moves from a suggested, but unproven, overexpression of ACE2 in patients with diabetes and/or arterial hypertension admitted to hospital with COVID-19, and the scarce evidence that these conditions independently increase the risk of mortality .12,13 Actually, SARS-CoV2 infection, rather than overexpressing, down-regulates ACE24 and the hypothesis that COVID-19 causes ACE2 overexpression lacks evidence. However, even speculating that ACE2 is overexpressed in these patients, the authors also assume that therapy with ACE inhibitors or ARBs can facilitate infection with COVID-19 and even increases the risk of developing severe and fatal COVID-19, because
both hypertensive and diabetic patients are most often treated with those medications. ACE2 overexpression, when it occurs, is most likely to be part of a defensive mechanism, and in the case of COVID-19 might be induced by the severe down-regulation caused by SARS-CoV2 binding.4 As a counter-regulatory system, ACE2 is one of the mechanisms through
which anti-RAS medications work to substantially reduce risk of cardiovascular disease due to hypertension and diabetes. ACE2 is indeed overexpressed in conditions associated with general or local harmful effects of AngII, such as heart failure and ischaemic heart disease.14,15 Experimental studies indicate that up-regulation of ACE2 might be a potent protective mechanisms against AngII-mediated organ damage. 16 There is no evidence that, because of the ACE2 overexpression, the SARS-CoV2 infection can be facilitated. Rather, there are opposite opinions derived from other

viral outbreaks.17 In Sierra Leone, Ebola infection has been empirically treated using a combination of ARBs and statins.18 Studies on influenza from the University of Virginia also suggest that these medications increase resistance to the effect of viral infections in general,17 and raise an interesting hypothesis about targeting with therapy individual resistance to infection more than reducing viral activity. Very recently, a strong hypothesis has been raised to make ACE2 a target for therapy against SARS-CoV2 infection.4 There is no evidence that the possibility of harmful effects of ACE inhibitors and ARBs is more than a mere speculation, despite being enormously amplified by both the conventional and social media, forcing the major international societies to issue position statements, though with different intensity. If real, the overexpression of ACE2 might be protective for the lung, by opposing the devastating effect of AngII,19 a speculation that has a much stronger pathophysiological basis. However, at the level of our knowledge, there is no evidence that this is true in subjects with SARS-CoV2 infection. A meta-analysis has been recently displayed in 'medRxiv', a web site making available papers, before peer review. In this analysis authors show that therapy with ARB might reduce substantially risk of COVID-19 severe disease (https://www.medrxiv.org/content/10.1101/2020.03.20.20039586v1). Hypertension carries a population-attributable risk of 35–40% for cardiovascular disease,20 and ACE inhibitors and ARBs are the most potent weapons that we have to fight against this killer. Disseminating speculations about a hypothetical risk associated with these medications, which does not have evidence or even strong pathophysiological support, does not help and in fact opens up the deleterious possibility of giving wrong and potentially dangerous recommendations to our patients,21 in a perspective dictated by defensive medicine. I think that doctors and major journals should be careful in raising speculation without a strong pathophysiological rationale, with potential devastating effects on public health programmes and individual well-being. Studies should be designed to establish whether protection can be provided by anti-RAS medications. Analysis of clinical records of SARS-CoV2 patients should be performed as soon as possible, to retrospectively look at the antihypertensive therapy and other confounders at the time of hospital admission.