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The puzzle of sharing bio-molecular targets between coronaviruses and mediators of the cardiovascular system in humans: Looking for plausible hypotheses

The emerging of SARS-CoV-2 and COVID-19 pandemia with a high mortality rate in older subjects with one or more known cardiovascular comorbidities [1] has prompted the question of "sharing bio-molecular targets" between coronaviruses and Renin Angiotensin Aldosterone System (RAAS), a system that is involved, at multiple levels, in the control of the cardiovascular function and, also, is a favorite drug target in cardiovascular diseases [2]. Indeed during treatment with Angiotensin-Converting Enzyme inhibitors (ACEi) and Angiotensin Receptor Blockers (ARBs) the known up-regulation of ACE2/Ang 1-7/MasR axes might be very useful to treat arterial blood pressure, ischemic heart disease and heart failure but, at the same time, detrimental since during COVID-19 it might open the route to SARS-CoV-2 that have been proven to use the ACE2 as functional receptor to enter the human cells [3]. This evidence at the bimolecular level has generated several commentary-style articles that claim it is more prudent to replace ACEi/ARBs during COVID-19 [2,4–6]. The main scientific societies have taken a critical position towards any therapeutic change in the absence of supporting data [7] and this is dictated by prudence. Nonetheless it should be said that switching can be done safely in arterial hypertension if the new drug is 1-well tolerated and a 2-good blood pressure control is achieved thus, during COVID-19, this switch, is again, a prudent position if we exclude to switch-off ACEi/ARBs in subjects with ischemic heart disease and heart failure [8] where we have no other valid therapeutic choices. Nonetheless a recent report claims that ACE2 is highly expressed in subjects with heart failure indicating a susceptibility to SARS-CoV-2 infection in these subjects [9] questioning, again, the idea of maintaining such therapy, even in people with heart failure.

This preamble clearly highlights the problem that is *coronaviruses competition with drugs targeting RAAS*, but the coin has two sides, and we don't know, till now, whether ACEi/ARBs might be detrimental or useful, thus the question is a little bit more complex and it seems necessary to produce sustainable hypotheses.

On the reasons of sharing.

(a) It is a "coincidence due to the spread-over-species and ancient-phylogeny" of Renin-Angiotensin System" [2]. This hypothesis is sustainable as RAAS is very diffuse over species and ACE2 expression in the airways makes it a possible target, but to prove.
(b) It is the consequence of the widespread use od drugs that increase ACE2 expression. This hypothesis is sustainable, exposing targets, especially in the airways where ACE2 is significantly expressed [10], may have facilitated the pathway to the coronavirus that, as any RNA viruses, exhibit a high mutation rate which guarantees the selection of efficient clones capable of infecting the host, but, again, to prove.
(c) It is a spillover from a laboratory. Leaving aside conspiracies on biological war, as we know, in the late nineties, developing strategies were aimed at modulating SRA at a genetic level, by using modified viruses targeting ACE2 to treat arterial hypertension and, more recently, to manipulate coronaviruses to better understand its virulence, are these strategies at the origin of the spillover? In a Correspondence to Nature Medicine Kristian G. Andersen et al. [11], states no with the phrase that I quote "It is improbable that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-like coronavirus". But "improbable" does not help us to remove all doubts, since we have learned the Popper's lesson: "one theory is scientific to the extent that can be disproved". Again, to prove.

On the effects of sharing.

(d) Is the high mortality rate for elderly subjects with the coexistence of comorbidities, among witch high blood pressure is present in more than 70%, related to the use of ACEi/ARBs? This is in theory possible but to prove. In the Italian subset of data from the Italian Health Institute [12] the use of ACEi/ARBs is documented in 52% and, obviously, not in 49%, thus, this is not a proof, we need more data and we asked Dr. Wei-jie Guan, the Author of one of the first report on COVID-19 in China [1], and he replied by email *"In our study, we did not record the use of ARBs given the urgency of data extraction. We do, however, believe that there is a need to investigate the association between the use of ACEI or ARB and the clinical outcomes of Covid-19. In fact, we are planning to conduct a clinical trial on recombinant ACE in patients with Covid-19"*. Finally, we have also data supporting potentials benefit of ACEi/ARBs on target organ damage [13] since RAAS is involved in the cytokine cascade and in the response to damage [14,15] thus we cannot exclude that the advantages outweigh the disadvantage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China [published online ahead of print, 2020 Feb 28]. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032.
[2] Ciulla MM. Coronavirus uses as binding site in humans angiotensin-converting enzyme 2 functional receptor that is involved in arterial blood pressure control and fibrotic response to damage and is a drug target in cardiovascular disease. Is this just a phylogenetic coincidence? [published on-line ahead of print, 2020 Mar 26]. J Med Virol 2020. https://doi.org/10.1002/jmv.25774.
[3] Liu Z, Xiao X, Wei X, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2 [published online ahead of print, 2020 Feb 26]. J Med Virol 2020. https://doi.org/

https://doi.org/10.1016/j.mehy.2020.109793
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10.1002/jmv.25726.
[4] Esler M, Esler D. Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic? [Published online ahead of print, 2020 Mar 11]. J Hypertens 2020. https://doi.org/10.1097/HJH.0000000000002450.
[5] Kuster GM, Pfister O, Burkard T, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? [Published online ahead of print, 2020 Mar 20]. Eur Heart J 2020. https://doi.org/10.1093/eurheartj/ehaa235. ehaa235.
[6] Roncati L, Gallo G, Manenti A, Palmieri B. Renin-angiotensin system: the unexpected flaw inside the human immune system revealed by SARS-CoV-2 [published online ahead of print, 2020 Mar 21]. Med Hypotheses 2020;140:109686. https://doi.org/10.1016/j.mehy.2020.109686.
[7] Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician.
[8] Ciulla MM. Switching to another antihypertensive effective drug when using ACEi/ARBs to treat arterial hypertension during COVID-19. Eur Heart J. (in press).
[9] Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2 [published online ahead of print, 2020 Mar 30]. Cardiovasc Res 2020. https://doi.org/10.1093/cvr/cvaa078. cvaa078.
[10] Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection [published online ahead of print, 2020 Mar 12]. Front Med 2020. https://doi.org/10.1007/s11684-020-0754-0.
[11] Andersen KG, Rambaut A, Lipkin WI, Holmes EC and Garry RF. The proximal origin of SARS-CoV-2. The proximal origin of SARS-CoV-2. Nature Med. https://doi.org/10.1038/s41591-020-0820-9.
[12] https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_20_marzo_eng.pdf.
[13] Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19 [published online ahead of print, 2020 Mar 27]. J Med Virol 2020. https://doi.org/10.1002/jmv.25785.
[14] Ciulla MM, Montelatici E, Ferrero S, et al. Potential advantages of cell administration on the inflammatory response compared to standard ACE inhibitor treatment in experimental myocardial infarction. J Transl Med 2008;6:30. https://doi.org/10.1186/1479-5876-6-30. Published 2008 Jun 12.
[15] Ciulla MM, Paliotti R, Esposito A, et al. Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. Circulation 2004;110(5):552–7. https://doi.org/10.1161/01.CIR.0000137118.47943.5C.

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