Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

The interplay of hypertension, ACE-2 and SARS-CoV-2: Emerging data as the "Ariadne's thread" for the "labyrinth" of COVID-19

Dr. William H. Stewart the US Surgeon General during 1965–1969 is remembered primarily for his infamous statement: "*It is time to close the book on infectious diseases …*" Five decades later, how erroneous this statement was! In 2020, humanity is facing one of the most devastating health urgencies in known modern history leading to health system collapse, economies "shutting down", unemployment surges and thousands of deaths worldwide due to COVID-19 infection.[1] For the cardiovascular medical community there are important issues to be clarified and in this editorial our attempt is to provide the latest evidence-based directions for the intriguing labyrinth-like associations of hypertension, renin-angiotensin system and COVID-19.

The hype of the hypertension link to COVID-19 pandemic was fueled by the initial reports from Wuhan, China, in which hypertension was present in 30% of cases and in 48% of non-survivors.[2] In 138 hospitalized patients with COVID-19, hypertension was observed in 31% (58% in intensive units)[3] and the official data from the National Health Commission of China demonstrate that 35% of patients diagnosed with COVID-19 have hypertension with the overall case fatality rate being 2.3% in the entire cohort but significantly higher (6%) in patients with hypertension.[4] The only available meta-analysis from Wuhan of 46248 cases, supports that hypertension constitutes the most prevalent comorbidity in 17% of patients infected with the novel coronavirus.[5] The globality of the pandemic stresses the need for international data. In Italy the most current analysis shows that of 69.1% of the deceased patients were hypertensives and 30% used angiotensin converting enzyme inhibitors (ACEIs) and 17% angiotensin receptor blockers (ARBs).[6] Despite the above observations, there are no robust data to suggest clearly an independent link of hypertension with increased COVID-19 morbidity and mortality.[7] Similarly, in other lower respiratory tract infections, diabetes and heart failure are independently related to adverse outcome, while hypertension *per se* is not.[7]

Major pathophysiological pathways by which COVID-19 causes cardiovascular and systemic complications is diffuse inflammatory response and ACE-2 (Fig. 1). The characteristic COVID-19 "cytokine storm" is reflected by increased IL-17, IL-7, IL-6, interferon-c, and TNFa.[7,8] Focusing on IL-6 it is associated with the outcome from the viral infection and also plays a key regulator role of immune-inflammatory response in essential hypertension.[7] Supportive to the latter, hypertension pathogenesis and progression of target organ damage is closely associated with low-grade inflammation[9] and this could partially explain the fact that hypertension is the most common comorbidity in COVID-19 cohorts and related to worst course of the infection.[7] The confounding effect, however, of ageing and other comorbidities like diabetes and renal dysfunction in this inflammatory link should be taken in mind with future studies urgently needed in this setting.

In humans, the entry of the new coronavirus into the target cells is facilitated by the spike protein that is anchored to the angiotensin converting enzyme-2 (ACE-2) in parallel with cellular serine protease TMPRSS2 actions.[7] ACE-2 converts angiotensin II to angiotensin 1-7 (Fig. 1).[10,11] Receptors of the ACE-2 are expressed in the epithelial cells of lungs, intestine, kidneys, heart and vessels and their activation causes vascular dilatation and provide renal and cardiovascular protection.[7,10,11] In this sense promoters of ACE-2 are studied as potential antihypertensive drugs.[10,11] The novel coronavirus SARS-CoV2 by using the ACE-2 "consumes" the enzyme and the protective actions of the latter are significantly attenuated. The non-counterbalanced actions of angiotensin II are partially responsible along with inflammation and thrombotic milieu to the COVID-19 related severe complications. At the level of the lungs the virus reduces the activity of the ACE-2 and regionally stimulates the renin-angiotensin system with leucocytes infiltration facilitation further accelerating the progression of the inflammatory response. In a relative study, COVID-19 patients were characterized by higher angiotensin II levels that were closely related to the total viral load and the degree of lung injury.[12] Recombinant ACE-2 administration has been proposed as a means to reduce angiotensin II levels and lung tissue lesions.[10,11] Concerning the heart and vascular component of COVID-19 infection, dysregulation of the ACE-2 related pathways are linked to cardiac muscle injury and potential hemodynamic collapse.[10,11]

Given consideration of the above, the "million dollars question", is about the effects of renin angiotensin blockers on ACE-2 expression/action and most importantly what is the clinical relevance of this modulation in humans in the context of COVID-19. There are data from animal studies for a more consistent upregulation of ACE-2 with the majority of ARBs, while the effect of ACEIs was variable.[7] This knowledge led to the opinion of potential susceptibility of patients on ACEIs and ARBs to COVID-19 infection[13] but this is currently unjustified. Firstly, the data in humans are scarce and only in the small intestine enterocytes upregulation of ACE-2 is reported due to ACEI.[14] Regarding the lungs there are zero evidence for humans and even if existed cannot directly lead to the conclusion that this upregulation can indeed facilitate viral cell entry.[7] If one wants to focus on pneumonia outside the COVID-19 setting, the use of ACEIs and ARBs reduces the risk of infection[15] and related mortality.[7]

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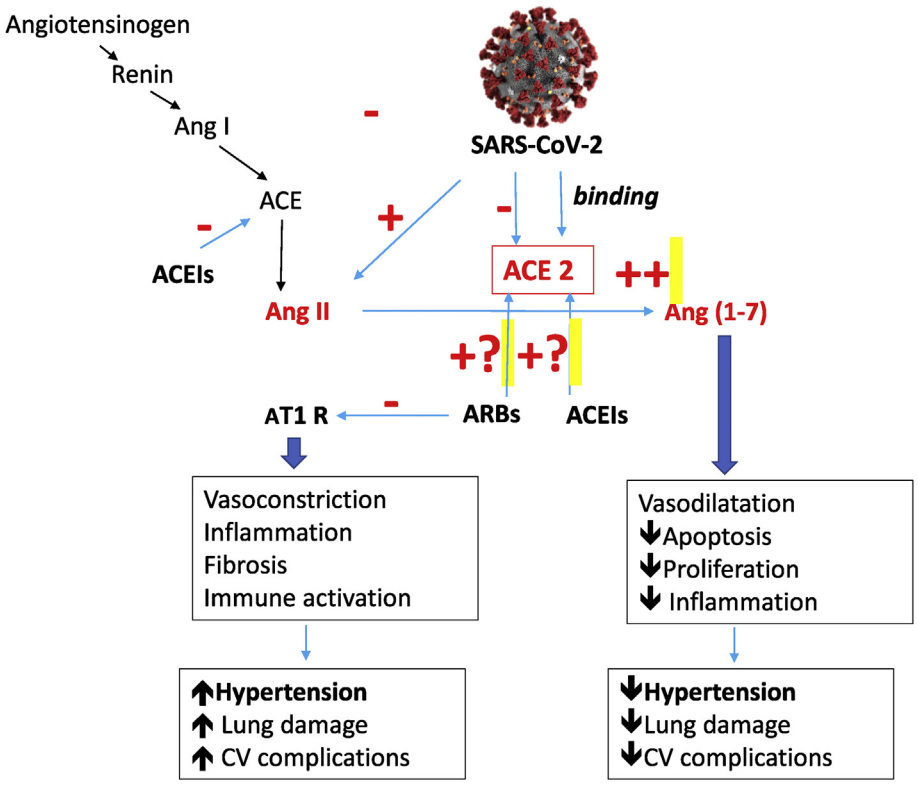

Figure 1. Pathophysiological pathways of SARS-CoV-2 and RAAS blockers.

In the era of COVID-19 "social distancing", the "scientific approaching" by rapid and free exchange of knowledge provides the scaffold for better therapeutic answers. We should be therefore thankful to the researchers for the important emerging data.[16-19] Firstly, Zhang P et al conducted a retrospective, multicenter study including 1128 adult patients with hypertension diagnosed with COVID-19 and admitted to hospitals in the Hubei Province.[16] They showed that the incidence of the 28-day all-cause death among hypertensives who had inpatient treatment with ACEIs/ARBs is significant lower compared with ACEI/ARB non-users (3.7% vs. 9.8%; $p = 0.01$).[16] Even after matching and adjusting variables in-hospital use of ACEIs/ARBs still exhibits remarkable association with reduced all-cause mortality. And even more recently, three simultaneous publications shed further light into the debate of renin-angiotensin therapies in the COVID-19 setting.[17-19] The work by Reynolds H et al showed that among 12594 patients who were tested for COVID-19 there was no association of ACEIs/ARBs with increased likelihood of a positive test or severe infection.[17] Further insight is provided by Mancia G et al focusing in 6272 cases with severe COVID-19.[18] After adjustment for confounders there was no independent association for the use of ACEIs/ARBs with susceptibility for infection or worse clinical outcome in contrast to loop diuretics that were linked to enhanced risk.[18] Interestingly the publication by Mehra M et al, included international data from 169 hospitals (11 countries in Asia, Europe, and North America) for 8910 patients with COVID-19 for whom discharge status was available.[19] There was no harmful association of either ACEIs or ARBs with mortality but also it was demonstrated that the use of statins and ACEIs was linked to less in-hospital deaths.[19] These findings clearly support recently published recommendations by many societies regarding continuation of ACEIs or ARBs among patients with co-existing hypertension, cardiovascular disease and COVID-19.[20,21] Moreover, they provide further rationale for ongoing studies with drugs targeting the renin-angiotensin system for therapy of COVID-19, like losartan for hospitalized (NCT04312009) and non-hospitalized patients (NCT043111177).[22]

There is a trending notion that there is not only a "second" wave of COVID-19 pandemic linked to the infection *per se* to be worried about but also a "third" and maybe a more important one! This "third wave" in the upcoming months and years is related to major events that would lead to a massive burden to the health systems because of COVID-19 related postponed guideline care in major disease states among them the cardiovascular ones. For hypertensive patients this is highly relevant due to the lack of regular follow-up along with destabilization of blood pressure levels due to unjustified discontinuation or modification of dosage of ACEIs/ARBs that can lead to heightened cardiovascular risk.[23] This outside-the-norm approach to chronic diseases might be a reaction of the public, as well as of some health providers, to the media-induced frenzy for the novel coronavirus. Attention should be paid to the latter phenomenon and the cardiovascular community has already played a key role on establishing guidance for treatment and continuity of care for high risk patients.[7,20] Interplay with the organization of the health systems and governments is needed to sufficiently address the "burden" of cardiovascular emergencies and routine cases throughout the COVID-19 era.

With clinical strength, and scientific rigor, the "labyrinth" of unanswered questions will be solved and the COVID-19 outbreak will be limited. Concerning hypertension therapy, it seems at present to be "immune" to COVID-19. Let's be optimistic and let the emerging data be our "Ariadne's thread".

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Conflict of interest

None.

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