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Relationship between ACE-inhibitors, ARBs and SARS-CoV-2 infection: where are we?

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Abstract:

SARS-CoV-2 is spreading rapidly all over the world. The case fatality rate seems higher in cardiovascular disease and hypertension. Other comorbidities do not seem to confer the same risk, therefore the understanding of the relationship between infection and cardiovascular system could be a crucial point for the fight against the virus. A great interest is currently directed towards the angiotensin 2 converting enzyme (ACE 2) which is the SARS-CoV-2 receptor and creates important connections between the virus replication pathway, the cardiovascular system and blood pressure. All cardiovascular conditions share an imbalance of the renin angiotensin system (RAAS) in which ACE 2 plays a central role. In the last few days, much confusion has appeared about the management of therapy with angiotensin converting enzyme inhibitors (ACE-i) and angiotensin receptor blockers (ARBs) in infected patients and in those at risk of critical illness in case of infection. In this article we will try to reorder the major opinions currently emerging on this topic.

Key words: SARS-CoV-2, COVID-19, ACE-inhibitors, ARBs, Cardiovascular disease

Introduction

SARS-CoV 2 (severe acute respiratory syndrome coronavirus 2) is spreading rapidly all over the world (1) and many scientists are making several efforts to reduce mortality of coronavirus disease-19 (COVID-19).

The case fatality rate (CFR) seems higher in some patients, in particular among those with pre-existing comorbidities, such as cardiovascular disease (CVD) (10.5%). Heart and Lung are closely tied, it is well known that pathological changes in lung parenchyma occurring in acute distress respiratory syndrome (ARDS) affect heart-lung interaction and could lead to worse consequences in patients with CVD. However, also patients with isolated hypertension have a high CFR (6%) which appears greater than cancer patients (5.6%) (2).

Since angiotensin-converting enzyme (ACE 2) has been identified as a SARS-CoV-2 receptor (3-4-5), much confusion has appeared about the relationship between SARS-CoV-2 and all those conditions that alter the renin-angiotensin-aldosterone system (RAAS) such as cardiovascular diseases and antihypertensive drugs.

Many doctors are now wondering how ACE-inhibitors (ACE-i) and angiotensin II receptor Blockers (ARBs) should be managed in patients infected with SARS-CoV-2 and in those at risk of infection. In this article we will try to review the major opinions currently emerging on this topic and on the relationship between cardiovascular diseases and COVID-19.

RAAS physiopathology

RAAS is a hormonal regulator of blood volume and systemic vascular resistance, involving kidneys, lungs, systemic vasculature, and the brain (6).

The angiotensin 1 converting enzyme (ACE) cleaves angiotensin I to generate angiotensin II, the peptide which binds to and activates angiotensin receptor subtype 1 (AT_1), resulting in vessel constriction. On the contrary, ACE 2 inactivates angiotensin II while generating angiotensin 1–7, a heptapeptide having a potent vasodilator function via activation of its Mas receptor, acting as a negative regulator of the renin–angiotensin system. (7-8-9). (**Figure 1**)

Furthermore, it was previously postulated that, in the acute respiratory distress syndrome (ARDS), ACE, angiotensin II, and angiotensin II receptor AT_1, promote the disease pathogenesis, whereas ACE 2 and the angiotensin II receptor AT_2 protect from ARDS (10).

ACE 2-SARS-CoV interaction

SARS-CoV-2 infection is due to the interaction between the spike protein (S) of the virus to ACE 2 (11), which is highly expressed in the heart and lungs, blood vessels, epithelial cells of kidney and intestine (12-13). Some authors, hypothesized that SARS-CoV causes robust downregulation of cellular ACE 2 expression levels, and it has been suggested that this mechanism is involved in the severity of disease (14).

Importantly, during SARS-CoV Emergency in 2003, some studies already showed the important role of ACE 2 and RAAS in Acute Lung Injury (ALI) due to SARS-CoV infection (3). Authors demonstrated a reduced ACE 2 expression induced by virus and an attenuation of acute lung failure by blocking RAAS pathway in mice (3).

ACE 2 and inflammation

In the above mentioned paper by Imai Y. et al (10), authors demonstrated that loss of ACE 2 expression in mutant mice resulted in enhanced vascular permeability, increased lung oedema, neutrophil accumulation, and worsened lung function. Importantly, treatment with catalytically

active recombinant ACE 2 protein improved the symptoms of ALI in both the Wild Type and ACE 2 knockout mice.

Furthermore, as mainly expressed in lungs, it was hypothesized that ACE 2 activity may influence endotoxin-induced des-Arg9 bradykinin (DABK)/B1 receptor signalling and neutrophil infiltration (15). In this mentioned paper, authors demonstrated that, after the exposure to inflammatory stimuli, ACE 2 activity is impaired, activating the DABK/BKB1R axis. This mechanism promotes the production and release of chemokines from airway epithelial cells, which recruit neutrophils to the lung. Authors demonstrated this mechanism in mice, after loss of ACE function due to endotoxin inhalation.

Moreover, in another previously published work (16), authors demonstrated that in mice with lipopolysaccharide (LPS)-induced acute lung injury (ALI), expression of ACE 2 was reduced, while an overexpression of ACE 2 regulates the ACE2/Ang-(1-7)/Mas and ACE/Ang II/AT_1 axes to balance the RAAS and attenuate inflammatory response.

From this point of view, ACE 2 seem to have a role in reducing inflammation and it has been suggested as a potential new therapy for inflammatory lung diseases.

Recently, starting from biological evidences which suggests that ACE inhibitors may increase the risk of lung cancer through the accumulation of bradykinin and substance P in the lung, it has been demonstrated that the use of angiotensin converting enzyme inhibitors was associated with a 14% increased risk of lung cancer (17).

ACE 2: localization and genetic polymorphism

ACE 2 expression in human tissues and apparatus

Even though ACE 2 is expressed on lung alveolar epithelial cells, enterocytes, endothelial cells of the blood vessels and arterial smooth muscle cells (18), his spike protein-binding site is mainly concentrated in type II alveolar cells (AT2), that express in turn many other genes that code for positive regulators of viral replication and transmission (19). Interestingly, as previously demonstrated by Jia and colleagues (20), ACE 2 expression correlates with the differentiation state of epithelia, being more expressed on the apical surface of polarized airway epithelia. Moreover, authors demonstrated that, undifferentiated cells expressing little levels of ACE 2 were barely infected with SARS-CoV, differently from well-differentiated cells.

ACE 2 genetic polymorphism (race and gender)

Considering the high variability of ACE 2 expression in different human tissues that reflect differences in their susceptibility to the infection, it was hypothesized that specific ACE 2 variants could reduce the association with S viral binding protein (21), and thus, genetic polymorphisms could determine different grade of susceptibility. Zhao et al (19), using single-cell RNA seq analysis, previously demonstrated that Asian male have a higher ACE 2 expression cell ratio than Caucasian and African-Americans. While Cai (22), using a RNA seq and micro array, indicated the absence of significant differences between both gender and race. Cao and colleagues (23) analyzed the coding-region variants in ACE 2 gene and the allele frequencies (AFs) expression from the ChinaMAP (China Metabolic Analytics Project, under reviewing) and 1KGP (1000 Genomes Project) databases. Authors did not find any proof of the existence of natural resistant variants for viral S-protein binding but differences in AFs distribution, probably related with a potential variability of ACE2 expression in different populations and ethnics in Asia. These results deserve further research in order to confirm ACE

2 role in ALI pathogenesis and a different susceptibility to SARS-CoV-2 infection among different populations (24). However, the genetic basis of ACE2 expression and function in different populations is still largely unknown.

For what concerns gender differences, some studies have shown how genetic differences of ACE 2 can be associated with a different cardiovascular risk, for some alleles only in women (25) for others in both sexes (26). Other studies have shown that different ACE 2 alleles are associated with an hypertensive phenotype in different ethnicities (27). The ACE 2 allele maps to the X chromosome, in an area that seems to escape random inactivation, a process that balances the gene expression linked to the X chromosome in women (28).

For this last reason and for other gender differences mentioned above, the hypothesis that ACE2 is among those responsible for gender differences in hypertension and ischemic heart disease cannot be excluded.

The COVID-19 CFR is now showing gender differences, with higher mortality in males (2). Also in this context it cannot be excluded that ACE 2 is implicated in the gender difference that characterizes the severity of the disease in case of SARS-CoV-2 infection. However, there are currently no studies examining this possibility.

ACE 2 and smoke habit

The above mentioned paper by Cai et al. (22) observed a significantly higher ACE 2 gene expression in smokers as compared with non-smoker. The mechanism involved in this altered expression of ACE 2 is still unknow, but authors postulated that smokers may be more susceptible to COVID-19, and that smoking history should be considered in identifying susceptible subjects. The main limitation of the mentioned study was that the analysed data

were from the normal lung tissue of patients with lung adenocarcinoma, which may be different with the lung tissue of healthy people.

ACE 2 activity and drugs

ACE inhibitors and angiotensin receptor blockers (ARBs) are widely employed in patients with arterial hypertension, heart failure and kidney disease (29). Although both classes of drugs act on the RAAS, ACE inhibitors inhibit the formation of angiotensin II and consequently the downstream effects mediated by both angiotensin II AT_1 (vasoconstriction, cell growth, sodium and water retention, sympathetic activation) and angiotensin II AT_2 receptor. The non-selective inhibition of angiotensin receptors, inhibit the breakdown of bradykinin and increase circulating bradykinin levels; this mechanism is involved in the pathogenesis of ACE inhibitors induced cough and angioedema (30). Conversely, ARBs have the specific target to displace angiotensin II from the AT_1 receptor and their associated autocrine cascade with bradykinin, nitric oxide, and vasoactive prostaglandins is considerably less important than that occurring with ACE inhibitor.

From the laboratory bench to the patient's bedside

Since it has been demonstrated that the binding of the SARS-CoV S protein to ACE 2 leads to ACE 2 downregulation (3) which results in an overproduction of angiotensin by ACE, it was postulated that this mechanism contributes to lung injury, because of an increased pulmonary vascular permeability due to a lower production of angiotensin 1–7 by ACE 2 (31).

Starting from the hypothesis regarding their anti-inflammatory effect, drugs causing ACE 2 up-regulation should be considered as protective. Ferrario et al (32) in 2005, studied a population of Lewis rats, 12 days after continuous administration of lisinopril, losartan or both, and demonstrated that selective blockade of either angiotensin II synthesis or activity, induced

increases in ACE 2 gene expression and ACE 2 activity. Moskowitz et al. in 2004 (33) postulated that both ACE inhibitors and ARBs might be considered as general viral antidotes, thanks to the attenuation of the cytokine in viral diseases. Recently, some authors hypothesized that, more specifically, angiotensin receptor 1 (AT_1) inhibitors might be beneficial for patients infected by COVID-19 who experience pneumonia (31-34-35), thanks to the demonstrated up-regulation of ACE 2 expression following chronic treatment (28 days) in rats (36). Indeed, as underlined above, ARBs, not only are related with ACE 2 up-regulation, but differently from ACE-inhibitors, seem to be not associated with increased bradykinin levels.

Conversely, considering the fact that, as described above, ACE2 is the common binding site for SARS-CoV-2, the suggestion to treat COVID-19 patients with AT_1 receptor antagonists for their associated ACE2 up-regulation seems counter-intuitive. The expression of ACE 2 is relatively contained in healthy subject, but it is increased in diabetics (37), and is substantially upregulated in hypertensive patients in therapy with ACE-inhibitors and ARBs (38). Respiratory symptoms related with SARS-CoV-2, are described to be more severe in patients with pre-existing CVD, often treated with RAAS inhibitors. Starting from this evidence, some authors (39-40), advanced the hypothesis that diabetic hypertensive patients treated with ACE inhibitors and ARBs, could be at higher risk of developing COVID-19 due to the increased specific receptor (ACE2) expression, even suggesting a therapeutic shift with calcium channel blockers (CCB).

Currently, there are not clear evidences demonstrating one of these two main hypothesis. Starting from the evidences about inflammatory mechanisms underlying ARDS pathogenesis during 2003 SARS-CoV emergency (24) it seems that, despite the protective role of ACE 2 up-regulation could seem paradoxical, it may protect patients against ALI rather than putting patients at higher risk to develop ARDS (31).

To note, is now starting the off-label experimentation of Tocilizumab (humanized monoclonal antibody against IL-6 receptor), to treat severe COVID-19 pneumonia sequelae.

In the last days, some cardiovascular scientific societies published their position statement about the possible discontinuation of ACE-inhibitors and/or ARBs in hypertension and/or heart failure in the context of COVID-19 outbreak **(Table 1)**. The European Cardiology Society (ESC), the Italian Cardiology Society (Società Italiana di Cardiologia: SIC), the Italian Hypertension Society (Società Italiana dell' Ipertensione Arteriosa: SIIA) and the European Society of Hypertension (ESH), highlighted the lack of any evidence regarding the harmful effect of ACE-i and ARBs in the context of COVID-19 outbreak. The main recommendation remains to not discontinue drug therapy in hypertensive and/or heart failure patients, both infected and at risk of critical illness in case of SARS-CoV-2 infection (41-42-43-44).

Conclusion

Although ACE 2 now appears to be the leading actor, the relationship between the cardiovascular system and COVID-19 is not yet well understood. Much caution should be exercised in the management of drugs that affect the renin angiotensin system, as there is no solid information. According to current evidences, official recommendations by ESC, ESH, SIC and SIIA recommend to not discontinue therapy in any setting of patient. We need epidemiological or preclinical studies that can give more certainties, with the hope of finding a mechanism to hinder the SARS-CoV-2 pathway.

Italians and Italian doctors: hold on!

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	Hypertension recommendation	**Heart failure recommendation**
Zheng et al. Nature reviews cardiology (5 March 2020)	Switch to other drugs is controversial	Not mentioned
SIC statement (11 March 2020)	Switch to other drugs is controversial	Benefit from their discontinuation is not documented
ESH statement (12 March 2020)	Available data do not support a differential use of RAS blockers	Not mentioned
ESC statement (13 March 2020)	Lack of any evidence regarding their harmful effect	Not mentioned
SIIA statement (13 March 2020)	Lack of any evidence regarding their harmful effect	Not mentioned

Table 1: Main recommandations by scientific community regarding the possible discontinuation of ACE-inhibitors and/or ARBs in hypertension and/or heart failure in the context of COVID-19 outbreak. *ESC: European Society of Cardiology, ESH: European Society of Hypertension, RAS: renin-angiotensin system, SIC: Società Italiana di Cardiologia, SIIA: Società Italiana dell'Ipertensione Arteriosa.*

Figure 1 legend: Role of ACE2 as renin angiotensin system regulator and SARS-CoV-2 binding site. *ACE: angiotensin converting enzyme, ACE-i: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers, AT_1: angiotensin receptor subtype 1, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2*