COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - Is there any scientific evidence for controversy?

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Abstract. AleksovaA, Ferro F, Gagno G, Cappelletto C, Santon D, Rossi M, Ippolito G, Zumla A, Beltrami AP, Sinagra G (University of Trieste, Trieste; National Institute for Infectious Diseases Lazzaro Spallanzani - IRCCS, Rome, Italy; University College London, London; University College London Hospitals NHS Foundation Trust, London, UK; and University of Udine, Udine, Italy). COVID-19 and renin-angiotensin system inhibition: role of angiotensin converting enzyme 2 (ACE2) - Is there any scientific evidence for controversy? (Review). J Intern Med 2020; 288: 410–421.

Renin–angiotensin system (RAS) blockers are extensively used worldwide to treat many cardiovascular disorders, where they are effective in reducing both mortality and morbidity. These drugs are known to induce an increased expression of angiotensin-converting enzyme 2 (ACE2). ACE2 acts as receptor for the novel SARS coronavirus-2 (SARS-CoV-2) which raising the important issue of possible detrimental effects that RAS blockers could exert on the natural history and pathogenesis of the coronavirus disease-19 (COVID-19) and associated excessive inflammation, myocarditis and cardiac arrhythmias. We review the current knowledge on the interaction between SARS-CoV-2 infection and RAS blockers and suggest a scientific rationale for continuing RAS blockers therapy in patients with COVID-19 infection.

Keywords: cardiovascular system, COVID-19, SARS coronavirus (CoV)-2, pandemic, angiotensin-converting enzyme 2 (ACE2), ACEIs/ARBs, RAAS.

Introduction

The past 2 decades have witnessed three lethal zoonotic diseases of humans caused by novel coronaviruses: the severe acute respiratory syndrome (SARS) in 2002, the Middle East respiratory syndrome (MERS) in April 2012, and currently, coronavirus disease-19 (COVID-19) caused by SARS-CoV, MERS-CoV and SARS-CoV-2, respectively. All three coronaviruses are listed in the WHO Blueprint list for priority pathogens [1]. Coronaviruses are members of the Coronaviridae family, a heterogeneous family of RNA viruses that cause respiratory tract infections in humans. HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1 cause mild infections whilst MERS-CoV, like SARS-CoV and SARS-CoV-2, can cause a spectrum of clinical manifestations from mild to severe disease and death [2].

The ongoing global pandemic of SARS coronavirus-2 (SARS-CoV-2) has affected almost 3 millions of people in all continents [3]. The high death rate has been attributed to comorbidities of diabetes, hypertension, coronary artery disease amongst others [4]. Renin–angiotensin system (RAS) blockers are extensively used worldwide to treat many cardiovascular disorders, where they are effective in reducing both mortality and morbidity. These drugs are known to induce an increased expression of angiotensin-converting enzyme 2 (ACE2).

SARS-CoV-2 binds to human cells via angiotensin-converting enzyme 2 (ACE2), which is expressed on epithelial cells of the lung, kidney, intestinal tract and blood vessels [5]. ACE2 expression is increased in patients with diabetes. Hypertension, treated

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with ACE inhibitors and ARBs, results in an upregulation of ACE2, which theoretically could enhance SARS-CoV-2 infection [6]. Therefore, since SARS-CoV-2 strongly interacts with ACE2, patients undergoing chronic RAS blocker treatment may be more prone to SARS-CoV2 infection or develop worse forms of COVID-19. In this review, we will discuss some aspects of the viral–cell interaction, pathophysiology and the ACEIs/ARBs action mechanism. Lastly, we suggest a scientific rationale for continuing RAS blockers therapy in patients with COVID-19 infection, thus providing both those clinicians working in the emergency setting and facing with acute cardiovascular diseases, and those following outpatients receiving ACEI/ARBs during the COVID-19 pandemic, a basis for their therapeutic decision-making.

Renin–angiotensin–aldosterone system blockade in cardiovascular diseases

As widely described in literature [7], the complex renin–angiotensin system (RAS) plays a crucial role in the pathophysiology of several morbidities, such as hypertension, diabetes mellitus, myocarditis [8], heart failure and myocardial infarction, where the use of RAS blockers is essential for management. ACE inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) delay or prevent the onset of heart failure in asymptomatic patients with left ventricular systolic dysfunction and, importantly, reduce both mortality and morbidity of patients with heart failure and reduced ejection fraction. In these patients, ACEIs/ARBs are titrated to the upper tolerated dose to achieve adequate RAS inhibition [9,10]. The most recent ESC guidelines recommend employing ACEIs/ARBs as antihypertensive treatment to prevent cardiovascular events and heart failure in diabetic patients, particularly in those with cardiovascular complications [11]. Also, ESC guidelines on hypertension give IA recommendation for employment of ACEIs and ARBs as antihypertensive drugs with demonstrated efficacy in blood pressure and cardiovascular events reduction [12]. Further, hemodynamic changes after an acute myocardial infarction cause a strong activation of both the circulating and the local RAS [13]. This adaptive response [14] could be dangerous and contributes to the development of cardiac structural and electrophysiological remodelling [15,16]. The effects of RAS inhibition are beneficial [17] in all patients after a myocardial infarction and are more prominent in more severe patients [18]. Further, in one systematic overview including 100,000 patients, it was observed that the most significant short-term survival benefit occurs if treatment with ACEIs is started within the first 7 days (40% in days 0 to 1, 45% in days 2 to 7, 15% subsequently) [19]. In line with this, guidelines provide class IA/IB recommendation to commence ACEIs/ARBs treatment within the first 24h after the acute event in all ST-segment elevation myocardial infarction (STEMI) patients with left ventricular systolic dysfunction, heart failure, anterior STEMI or diabetes [18,20]. Treatment with ACEIs/ARBs is also recommended (class IA/IB) in non-ST-segment elevation myocardial infarction (NSTEMI) patients with left ventricular systolic dysfunction, heart failure, hypertension or diabetes mellitus, in order to reduce mortality and risk of recurrent ischaemic event or hospitalization for heart failure [21,22].

Angiotensin-Converting enzyme 2 (ACE2)

In the context of SARS-CoV-2 infection, it is important to note that ACEIs/ARBs increase the local expression and activity of angiotensin-converting enzyme 2 (ACE2) [23], a zinc metalloprotease that exists both as a membrane-associated form and as a secreted form. ACE2 is ubiquitously expressed, with the highest levels of transcripts being found in the lung, the heart and the gastrointestinal and urinary systems. ACE2 is mostly expressed in lung alveolar type II (AT2) cells, myocardial cells, vascular endothelia, buccal epithelial cells, T and B lymphocytes, on the proximal tubule epithelial cells in the kidney, and in testes [24,25]. All cardiac cell components (i.e. endothelial cells, smooth muscle cells, cardiac myocytes, fibroblasts and macrophages) express ACE2, although the highest levels were observed in vascular cells, especially pericytes [26,27]. Upregulation of ACE2 expression has been documented in patients affected by myocardial infarction or heart failure. However, in animal models of ageing, pressure overload and chronic ischaemia, ACE2 downregulation has been associated with cardiac hypertrophy, adverse remodelling and fibrosis [28-30]. Conversely, ACE2 expression is reduced in hypertension, advanced diabetes mellitus and atherosclerotic plaques and, experimentally, by both angiotensin II (Ang II) and endothelin [28-31]. Importantly, it has been estimated that heritability accounts for 67% of the variability in ACE2 circulating levels. Moreover, ACE2 genetic variants have been associated with both essential hypertension and coronary heart disease (CHD), whilst they act as disease modifiers.
of both hypertrophic and dilated cardiomyopathies [31]. Concerning development, it was shown that ACE2 protein levels and activity are high during gestation and decline postnatally [32].

ACE2 acts as a negative regulator of RAS, by degrading AngII to the heptapeptide angiotensin 1-7 (Ang1-7) [33], that exerts its biological activity via the Mas receptor, modulating the release of nitric oxide (NO), antagonizing the intracellular effect of AngII stimulation (thus tempering the production of reactive oxygen species), at least in part by activating intracellular phosphatases [34]. As a result, Ang1-7 exerts many positive effects on the cardiovascular system (e.g. increased endothelial function, reduced fibrosis, anti-proliferative effects on smooth muscle cells, anti-cardiac hypertrophy), as well as on other organs, such as the lungs, where it exerts anti-fibrotic, anti-inflammatory and anti-apoptotic effects [35-37]. Moreover, ACE2 cleaves other peptides and plays a central role in inactivating des-arginine(9)-bradykinin (des-Arg(9)-BK), a potent metabolite of the kinin-kallikrein system that increases vascular permeability, thus promoting angioedema, acting on B1 type receptors, which are, in turn, upregulated by inflammatory cytokines [38,39]. According to some authors, the leakage of plasma in the subendothelial compartment in conjunction with the inflammatory response triggered by the host–virus interaction may have a central pathogenetic role in the endotheliitis and disseminated intravascular coagulation that have been documented to occur in COVID-19 patients [39-41]. ACE2 plays an important role in heart failure, in diabetic microvascular or macrovascular disease [42] and in inflammatory lung disease [43], and ACEIs/ARBs-mediated increase in ACE2 exerts a protective role in many conditions such as atherosclerosis, myocardial infarction, myocardial dysfunction, heart failure, diabetes mellitus and acute lung injury (ALI).

SARS-COV-2 infection and host injury

Although the details have not been completely elucidated yet, SARS-CoV-2 was originated either as a result of natural selection that took place in a host before zoonotic transfer or by natural selection in humans after the zoonotic transfer had occurred [44,45]. Importantly, during the selection process, the virus acquires a furin cleavage site and three predicted O-linked glycans around the site that are very likely associated with the acquisition of a highly pathogenic phenotype [44].

Virus – entry and spread

Coronaviruses’ (SARS-CoV, SARS-CoV-2) Spike (S) protein, binds with high affinity to human ACE2 [45] (Figure 1). Before SARS-CoV-2 and SARS-CoV cell entry, their S protein is subjected to a priming process via serine protease TMPRSS2 in order permit the attachment of viral particles to ACE2 and thus on cell surface [46]. This entry mechanism is confirmed by the fact that TMPRSS2 inhibition or TMPRSS2-KO mice show both decreased, though not abolished, S protein priming, and reduced viral entry, spread, and inflammatory chemokine and cytokine release [46,47]. SARS-CoV-2 is then internalized mainly by endocytosis. In this process, phosphatidylinositol 3-phosphate 5-kinase (PIKfyve), two pore channel subtype 2 (TPC2) and cathepsin L are critical for virus entry [48]. SARS-CoV binding also induces the release/shedding of catalytically active ACE2 ectodomains via ADAM-17/TACE activity [49-52]. In line, inhibition of ADAM17/TACE blocks ACE2 shedding and limits viral entry in both in vitro and in vivo [53]. Intriguingly, recent data show that soluble ACE2 (sACE2) could inhibit S-mediated infection in vitro. Although sACE2 was not able to completely abrogate viral entry, ACE2 shedding may help in contrasting viral diffusion to different organs [54]. Conversely, it has been demonstrated that ACE2 downregulation following infection has a detrimental effect in the pathogenesis of ALI [55], although this effect could be limited, judging by the amount of ACE2 expressed by the AT2 cells of the lungs, or the ratio between ACE2 and circulating ACE2 [24,56,57]. Altogether, these results suggest that ACE2 might not be the only receptor for SARS-CoV-2. In fact, recent structural and predictive studies proposed other receptor-mediated mechanisms for SARS-CoV-2 cell entry, indicating three other aminopeptidases, alanyl aminopeptidase (ANPEP), glutamyl aminopeptidase (ENPEP) and dipeptidyl peptidase 4 (DPP4), as the most probable additional receptors [58,59].

Virus-direct negative effects

It is known that the virus survival strategy is to elude and suppress host innate immune defences through gene deactivation or inhibition [57,60,61]. In line, Huang et al. demonstrated that SARS-CoV nonstructural protein (nsp1) binding to ribosomes
Figure 1  The figure summarizes SARS-CoV, and presumably SARS-CoV-2, confirmed and hypothesized mechanism of viral binding, internalization and shedding via ACE2 interaction, and the successive downregulative effect on ACE2 and the resulting pathogenic effect on lung and cardiac tissues. Abbreviations: angiotensin-converting enzyme 2 (ACE2); angiotensin (Ang); angiotensin 1-7 (Ang 1-7); transmembrane protease, serine 2 (TMPRSS2); ADAM metallopeptidase domain 17 (ADAM-17); tumour necrosis factor-α converting enzyme (TACE); SMAD family member2, 7 (SMAD2, SMAD7); nonstructural protein 1 (nsp-1); SARS-CoV nucleocapsid (N) protein (N protein); interleukin-2, 7, 10 (IL-2, 7,10); granulocyte colony-stimulating factor (G-CSF); transforming growth factor-α (TNF-α); monocyte chemoattractant protein 1 (MCP-1).
inhibits host gene translation [62]. More precisely, a marked downregulation of ACE2 mRNA and protein expression was associated with the presence of SARS-CoV and (HCoV)-NL63 (another human coronavirus, causing mild to severe respiratory tract infections, excluding SARS) in target tissues [63]. However, whilst SARS-CoV induced ACE2 shedding from the cell surface, (HCoV)-NL63 did not, suggesting that ACE2 shedding is directly related with prognostic severity [30,52,53]. Additionally, a viral titre- and infection time-related SARS-CoV effect on ACE2 mRNA has been shown, where lower viral titre is associated with upregulation instead, higher dosage and time after infection are correlated to reduced ACE2 expression [64]. Last, since interleukin (IL)-2, IL-7, IL-10, G-CSF, IP-1 MCP-1 MIP-1α and TNF-α are highly increased in patients with severe SARS-CoV infection, with respect to patients with mild symptoms, it was hypothesized that ACE2 suppression could result from a direct cell driven effect, rather than virus mediated. In line, in vitro data could support a suppressive role for IL7 and IL2 on Ace2 expression [64].

Acute Lung Injury – ALI

Part of the conundrum related to the role of ACE2 in SARS-CoV-2 infection (designated coronavirus disease-19 or COVID-19) is related to the role exerted by this enzyme in ALI. Indeed, ALI that can be caused by a number of aetiopathological agents (e.g. influenza and coronaviruses, bacterial pneumonia, sepsis [65], cigarette smoking [66], particulate matter [67] and aspiration pneumonia [68]) has been associated with the activation of the local RAS [69]. Ang II, by acting on AngII type 1 receptor (AT1R), activates several signal transduction pathways, including mitogen-activated protein kinase (MAPK) and Janus-activated kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), phosphatidylinositol 3 kinase (PI3K), promoting vascular permeability, vasoconstriction, myofibroblast, smooth muscle cell and macrophage activation, fibrosis, and the expression of inflammatory cytokines [65,70,71]. The latter effect has been mainly attributed to the ability of AngII to activate the transcription factor NFκB via AT1R [72]. AngII may also bind to other receptors, the most studied of which is type 2 receptor (AT2R). However, the net effect of AT2R stimulation is less clear since both pro- and anti-inflammatory effects have been described [57]. To corroborate the crucial role exerted by pulmonary RAS on ALI, it was shown that AngII levels are increased in animal models of ALI [73]. Importantly, recent reports on SARS-CoV-2-infected patients showed a significant increase in Ang II plasma level that was inversely correlated with viral load [74]. In line, survivors of acute respiratory distress syndrome (ARDS) have been associated with lower plasmatic ACE levels, in a preliminary report [75]. Moreover, by evaluating the levels of angiotensinogen metabolites, it was shown that ARDS outcome was associated with higher Ang1-9/Ang1-10 and Ang1-7/Ang1-10 ratios, suggesting higher activity of both ACE and ACE2 in survivors [76]. Conversely, AT1R blockage resulted in the protection of animal models of lung injury [77]. Further, an accumulating body of literature is showing the protective role exerted by ACE2 on ALI. Indeed, ACE2 knockout animals develop more severe forms of ALI in response to a series of injurious stimuli [67,73,75]. Conversely, the results of clinical trials that experimented the administration of soluble ACE2 to treat patients suffering from ARDS, although in early phase and not designed to test efficacy, did not show very promising results [78]. Moreover, as anticipated, ACE2 downregulation causes also accumulation of des-Arg(9)-BK, which interacts with type B1 bradykinin receptor, possibly leading to the observed development of angioedema, and coagulation cascade triggering [39]. Last, the protective effect of ACE2 may be also postulated considering both that ACE2 levels decrease with age and that, although children are vulnerable to the infection, these patients are usually less severe [79].

Myocardial injury

The relevance of myocardial involvement in SARS-CoV-2 infection is related to the high frequency of patients showing evidence of acute cardiac injury, especially amongst those that necessitated ICU care [80]. This finding is similar to that observed in patients that succumbed to the SARS crisis in Toronto, where the duration of disease was almost 10 times shorter in patients that showed cardiac involvement vs. those that had no evidence of cardiac infection [30]. In line, a recent report suggests that the SARS-CoV-2 infection can be complicated by acute fulminant myocarditis [81]. In this scenario, left ventricular function completely recovered early after immunomodulation therapy [82] suggesting that organ damage in these patients is more the consequence of a ‘cytokine storm’, than of an uncontrolled viral replication [80,82,83]. To complete the picture, the presence of...
viral particles infecting myocardial interstitial cells, but neither endothelial cells nor myocytes, was recently described to occur in one patient that died of COVID-19, with a clinical scenario characterized by respiratory distress, hypotension and cardiogenic shock [84].

Consistently, SARS-CoV-2-infected patients were characterized by high amounts of plasmatic IL1β, IFNγ, IP10 and MCP1 levels. Additionally, more severe patients had higher concentrations of G-CSF, IP10, MCP1, MIP1A and TNF-α, strongly supporting the relevance of cytokines in dictating prognosis [80]. This observation has stimulated early trials experimenting IL6 axis inhibition in COVID-19 patients [82]. Cytokine-mediated systemic response to infections can be associated with transient cardiac dilatation and dysfunction [85]. However, local viral replication could depress cardiac function too. Indeed, SARS-CoV can activate the NLRP3 inflammasome [86], thus promoting the release of IL1β and possibly IL18, a mediator of acute inflammation and tissue destruction, which can trigger a proinflammatory cascade leading to myocarditis [87].

The gender difference in mortality could be related to the smoking prevalence and sex-based immunological differences. Moreover, a recent study suggests that ACE2 expression seems to be higher in women than men and to decrease with age [64,96,97]. The more severe prognosis of patients of older age may also been related to distinct mechanisms, such as the age-associated decline in the molecular machinery involved in removing cytosolic DNA [98]. Also, patients with hypertension or diabetes show high rate of ACE2 genetic polymorphism that could influence ACE2 or Ang1-7 expression [84]. The advent of ACE2 genetic polymorphism that could influence ACE2 or Ang1-7 expression may be reduced both by the binding of SARS-CoV to ACE2, leading to the endocytosis of the latter [91], and as a result of the activation of ADAM-17/TACE by SARS spike protein, known to cleave, internalize and promote ACE2 shedding in endothelial cells [49]. Downregulation of ACE2 results in an unbalance between the detrimental action of AngII and the cardioprotective effects of Ang1-7. Further, more chronic negative consequences on the cardiovascular system might be related to ACE2 downregulation via des-Arg(9)-BK accumulation and its consequential increase in vascular permeability, inflammation that leads to an increased atherosclerotic plaques formation [92]. Further, ADAM-17/TACE activation, induced by the spike protein, promotes TNF-α release, thus increasing macrophage mobilization and activation [49,52]. Moreover, SARS-CoV nucleocapsid (N) protein potentiates TGF-β-mediated fibrosis [93].

ACEIs/ARBs treatment during the COVID-19 pandemic

On the basis of the increase of ACE2, associated with ACEIs/ARBs treatment, it has been speculated that these drugs might rise the chances of severe COVID-19 [94]. According to the last report (29th April 2020) from the Italian Istituto Superiore di Sanità, 25,452 patients positive to SARS-CoV-2 died. The observed mortality was higher amongst males in all age groups and in patients with comorbidities. In 9.23% of the total sample, data regarding comorbidities were available; 81.7% of the deceased patients had 2 or more comorbidities, such as arterial hypertension (69.2%), diabetes mellitus (31.8%) and CHD (28.2%). Similar data regarding comorbidities and gender differences in mortality were observed during China COVID-19 emergency [95]. Prior to hospitalization, 24% of COVID-19-positive deceased Italian patients were on treatment with ACEIs and 16% were receiving ARBs.

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7 levels in the human body [64,99-101]. Therefore, a negative correlation between ACE2 expression and mortality has been suggested [64].

Should indications for ACEIs/ARBs treatment change for patients with COVID-19?

An enormous body of literature shows that ACEIs/ARBs should be given as early as possible to all patients with acute myocardial infarction, in asymptomatic patients with left ventricular systolic dysfunction, in patients with heart failure and reduced ejection fraction, as well in hypertensive or diabetic patients, for their important benefits for patient survival. Conversely, an abrupt discontinuation of ACEIs, in survivors of myocardial infarction on long-term treatment [102,103] or in patients with heart failure [104], can be potentially harmful. Further, at the time of this pandemic COVID-19, there are no experimental or strong clinical data to contraindicate this therapy whilst, on the contrary, some are supporting the opposite [105,106].

Calcium channel blockers were suggested as alternative treatment for ACEIs and ARBs [107]. However, since the development and progression of the remodelling process after an myocardial infarction, in setting of heart failure, hypertension or diabetes mellitus depends on neurohormonal activation, only medications, which block the effect of neurohormones [108], have demonstrated to reduce morbidity and mortality of patients. For calcium channel blockers, in spite of their beneficial hemodynamic activities, there is no evidence supporting their ability to exert favourable effect early after an acute myocardial infarction on preventing heart failure in diabetics with hypertension and on general mortality reduction [18,109,110]. Lastly, calcium channel blockers have a strong interaction with antiviral drugs (lopinavir/ritonavir) used to treat COVID-19 patients.

In a recent retrospective observational study from Wuhan, including 188 hypertensive subjects affected by COVID-19, treatment ACEIs/ARBs was associated with lower all-cause mortality [105]. Furthermore, a large population-based case-control study performed in Lombardy during the ongoing COVID-19 epidemic spread on more than 6000 COVID-19 patients did not show evidence that the use of either ARBs, or ACEIs, affects the risk of COVID-19 infection [111]. Italian Regulatory Agency (AIFA) recommended on 17 March 2020 do not to modify the therapy in progress with anti-hypertensives (whatever the therapeutic class) in well-controlled hypertensive patients, as they expose frail patients to potential new side effects or an increase in risk of adverse cardiovascular events does not appear justified. For the same reasons, compared to the hypothesis of using ACE inhibitors and sartans also in healthy people for prophylactic purposes, remembered that these drugs should be used exclusively for the treatment of pathologies for which there are approved [112].
Conclusions

As depicted in Figure 1, the interaction between SARS-CoV-2 and the host cell promotes a series of complex alterations leading to both the downregulation of ACE2 expression and the increased production and release of inflammatory cytokines. The net loss of the ACE2/Ang1-7 anti-inflammatory properties, along with a dysregulated vascular permeability ACE2/des-Arg(9)-BK mediated and the pro-inflammatory properties of secreted cytokines, may be therefore responsible for a large part of the detrimental effects caused by COVID-19. Taking into account, the evidences presented in this review, and at present, there are no data demonstrating adverse outcomes amongst COVID-19 patients in therapy with ACE/ARBs; on the contrary, it seems that the treatment discontinuation could have plausible negative effects. Thus, according with the recommendations of the main cardiovascular international [113,114] and Italian scientific societies [115,116], patients chronically taking ACE/ARBs who contract COVID-19 infection should not discontinue the treatment, neither temporarily (Figure 2). Further researches are needed to indagate some uncleared and controversial aspects of the pandemics.

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Author contribution

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Conflict of interest statement

All authors declare no conflicts of interest.

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