The Cross-Talk between Age, Hypertension and Inflammation in COVID-19 Patients: Therapeutic Targets

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Abstract
This paper presents a brief overview of the complex interaction between age, hypertension, the renin–angiotensin–aldosterone system (RAAS), inflammation, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection. Coronavirus disease 2019 (COVID-19) is more frequent and more severe in comorbid elderly patients, especially those with hypertension, diabetes, obesity, or cardiovascular diseases. There are concerns regarding the use of RAAS inhibitors in patients with COVID-19. Some physicians have considered the need for interrupting RAAS inhibition in order to reduce the possibility of SARS-CoV2 entering lung cells after binding to angiotensin-converting enzyme 2 (ACE2) receptors. We offer a different point of view in relation to the need for continuing to use RAAS inhibitors in patients with COVID-19. We focused our article on elderly patients because of the distinctive imbalance between the immune response, which is depressed, and the exacerbated inflammatory response, ‘inflammaging’, which makes the geriatric patient an appropriate candidate for therapeutic strategies aimed at modulating the inflammatory response. Indeed, COVID-19 is an inflammatory storm that starts and worsens during the course of the disease. During the COVID-19 pandemic, various therapeutic approaches have been tested, including antiviral drugs, interferon, anti-interleukins, hydroxychloroquine, anti-inflammatories, immunoglobulins from recovered patients, and heparins. Some of these therapeutic approaches did not prove to be beneficial, or even induced serious complications. Based on current evidence, in the early stages of the disease modulation of the inflammatory response through the inhibition of neprilysin and modulation of the RAAS could affect the course and outcome of COVID-19.

1 Introduction
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has spread quickly around the world, causing clusters of prevalent respiratory Coronavirus Disease 2019 (COVID-19), including acute respiratory distress syndrome (ARDS), and becoming a serious public health concern [1]. From the beginning of the COVID-19 pandemic to date, there has been a continuous updating of the pathogenetic mechanisms of the disease. From clinical, epidemiological, and radiological criteria, attention has been paid to the demodulation of the renin–angiotensin–aldosterone system (RAAS) and inflammation. At present, there are no therapeutic recommendations applied worldwide. The counteracting of RAAS demodulation and inflammatory storm appear to be optimal approaches.
The purpose of this review is to clarify the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in elderly patients with COVID-19. The high prevalence of heart failure in elderly patients and the coexistence of cytokine storms in patients with COVID-19 may be the opportunity to switch therapy with ACEIs or ARBs to sacubitril/valsartan to exploit the anti-inflammatory potential of neprilysin inhibition and RAAS modulation.

A comprehensive literature search was performed through MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, PubMed, and the Cochrane Central Register of Controlled Trials were searched through the Ovid interface to identify English-language articles published from 1 December 2019 to 29 May 2020. In all electronic databases, the following search strategy was implemented and the following keywords (in the title/abstract) were used: ‘COVID-19’, ‘SARS-CoV-2’, ‘coronavirus’, ‘angiotensin-converting enzyme 2’ OR ‘ACE2’, ‘renin–angiotensin–aldosterone system’ OR ‘RAAS’, ‘angiotensin-converting enzyme inhibitors’ OR ‘ACEi’, ‘angiotensin-receptor blockers’ OR ‘ARBs’, ‘Elderly’ OR ‘Older Adults’, ‘Hypertension’, ‘Cytokines’ OR ‘ACE2’, ‘angiotensin-converting enzyme inhibitors’ OR ‘ACEi’, ‘angiotensin-receptor blockers’ OR ‘ARBs’, ‘Elderly’ OR ‘Older Adults’, ‘Hypertension’, ‘Cytokines’ OR ‘ACE2’, ‘angiotensin-converting enzyme inhibitors’ OR ‘ACEi’, ‘angiotensin-receptor blockers’ OR ‘ARBs’.

Regular alerts were also established. The electronic search strategy was complemented by a direct, manual review of the references. Search results were combined and duplicates removed. Studies were first screened on the basis of title and abstract, and the full text was then reviewed. Two reviewers (DA and GC) independently performed the revision, while discrepancies were solved by consensus, involving an additional author (RAI). The methodological quality of the included studies was assessed by the authors. No statistical analysis was conducted due to the heterogeneity of the selected papers. Some data were obtained from both human and animal studies, and this invalidates the direct transfer of conclusions from animals to humans.

2 Potential Confounding by Age and Hypertension in Coronavirus Disease 2019 (COVID-19) Patients

2.1 COVID-19 and Older Adults with Comorbidities

Older people, often frail and with several comorbidities, are at highest risk for severe and fatal forms of COVID-19 [2–4]. Experience from Italy shows a median age at death of 79 years for men and 82 years for women [5]. On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a ‘pandemic’, and on 2 April 2020, the death rate was double that of severe acute respiratory syndrome (SARS) in 2002–2003 and Middle-East respiratory syndrome (MERS) in 2013 combined. This pandemic seemed to be expanding at an exponential rate, doubling the number of positive cases every 43 h.

New COVID-19 populations are generally liable, but elderly people with underlying diseases are more susceptible. Diabetes, hypertension, obesity, cardiovascular disease, and cerebrovascular disease are the most important comorbidities involved in the degeneration of clinical conditions of patients with COVID-19 [3, 4, 6, 7]. The elderly are more prone to SARS-CoV-2, are more frequently admitted to intensive care units (ICUs), and have higher mortality rates [8, 9]. Yang et al. [10] found that 52% of their COVID-19 population was older than 60 years of age and were more likely to have chronic medical illnesses. Similar results were also published by Yang et al. [11].

2.2 COVID-19 and Hypertension

Hypertension has been detected as a common comorbidity in viral pneumonia and is already one of the most relevant features associated with mortality, before the COVID-19 pandemic [12]. These data have also been confirmed in COVID-19 pneumonia [13, 14]. Nevertheless, a lack of sound evidence that hypertension per se is an independent risk factor for COVID-19 has recently been demonstrated [15]. Potential confounding by age when hypertension was evaluated as a risk factor for the severity of COVID-19 infection has been underscored [16].

SARS-CoV2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to infect host cells [17]. ACE2 is a key enzyme in the renin-angiotensin system [18, 19] that regulates blood pressure, fluid and electrolyte balance, and systemic vascular resistance [20]. The strong inhibition of ACE2 by SARS-CoV2 may increase the levels of angiotensin II (Ang II) in the alveolar tissue of the lung, leading to increased vascular permeability and pulmonary edema [21, 22].

In experimental models of hypertension and diabetes, ACE2 enzyme expression was shown to be downregulated. As a consequence, tissue Ang II levels were significantly increased, contributing to hormone-mediated tissue injury and supporting the fact that ACE (enzymatic core of RAAS, which converts Ang I hormone into the active vasoconstrictor Ang II) and ACE2 have counter-regulatory functions [23, 24]. ACE2 messenger RNA (mRNA) is mainly detected in the small intestine, colon, duodenum, kidney, testis, and gallbladder. The overall expression of ACE2 in the lungs is low but it may be upregulated under certain conditions, such as asthma and idiopathic pulmonary fibrosis [25, 26]. Tissue hypoxia associated with myocardial infarction and cirrhosis may also increase ACE2 expression in both humans and rats [27, 28]. Animal
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studies have shown that medications commonly used for hypertension and heart disease to regulate the RAAS, such as ACEIs and ARBs, may increase the expression of ACE2 proteins [29, 30]. It has also been suggested that a population with higher ACE2 expression might be more susceptible to SARS-CoV2 [31]. Furthermore, ACE2 polymorphism could increase the risk of COVID-19 in patients treated with ACEIs or ARBs [32]. Moreover, a very high affinity binding of SARS-CoV2 for ACE2 could explain the low viral burden required to infect a host cell [33]. Nevertheless, ACE2 knockout mice displayed more severe symptoms of ARDS, while overexpression of ACE2 had some protective effects [34]. Based on the assumption that compensation of ACE2 and balancing of the ACE/ACE2 function may be a way to alleviate virus-induced severe lung injury, Wu suggested testing ACEIs and ARBs to reduce SARS-CoV2 respiratory symptoms [35]. Furthermore, inhibition of the Ang I/Ang II/angiotensin type 1 receptor (AT1R) pathway alleviated inflammatory lung disease [36], and losartan (an ARB drug) administration improved pulmonary vascular remodeling, inhibited smoke-induced right ventricular systolic pressure and Ang II elevations, and partially reversed ACE2 decrease in rat lungs [37]. Moving from theory to practice, ACEIs and ARBs have recently been reported as independent predictors of lower plasma ACE2 concentrations [38]. On the other hand, a first retrospective study did not show any significant differences in fatal outcomes of a limited number of hospitalized COVID-19 patients regardless of whether or not they were receiving ACEI/ARB treatments [39]. Since then, several observational studies have confirmed that ACEI/ARB use does not make COVID-19 patients more vulnerable to the virus [40–45]. Nevertheless, when an effect of the ACEI/ARB therapy was detected in COVID-19 patients in these and other studies, it was shown to be more protective than harmful [46–48].

Serious clinical presentations of SARS-CoV-2 infections are generally associated with rapid viral replication, infiltration of inflammatory cells, and exaggerated release of cytokines (cytokine release syndrome), resulting in multiorgan damage, including ARDS [51, 52]. Patients admitted to ICUs have higher serum levels of monocyte chemoattractant protein-1, granulocyte colony-stimulating factor, granulocyte–macrophage colony-stimulating factor, macrophage inflammatory protein-1A, interferon-inducible protein-10, and tumor necrosis factor (TNF)-α [53], suggesting that the ‘intensity’ of the ‘cytokine storm’ modulates the severity of the disease. Beyond the cytokine storm, the lymphocyte count has also been associated with increased disease severity [54].

The SARS-CoV-2-induced imbalance of ACE2/ACE results in AT1R-mediated inflammatory response with activation of the complement system, mitogen-activated protein kinases (MAPK) and nuclear factor kappa B (NF-kB). The decrease in Ang-(1–7) following SARS-CoV-2-mediated ACE2 downregulation seems to play a pivotal pathogenic role. Thus, Ang-(1–7) should be considered an anti-inflammatory molecule modulating the NF-κB, MAPK, and ERK1/2 pathways. This confirms the view that drugs able to increase Ang-(1–7) could benefit SARS-CoV2 patients.

4 Age as a Potential Driver of Interventions Targeting the Renin–Angiotensin–Aldosterone System (RAAS)

Age likely plays a key role as a modulator of the interaction among factors potentially affecting the course of COVID-19. Indeed, ‘inflammaging’, a type of dysregulated immune response with an exacerbated inflammatory and depressed immunologic component, is a typical feature of aging and may make the elderly more vulnerable to COVID-19, mainly by promoting the cytokine storm [55]. Interestingly, the resistance of bats to the toxic effect of COVID-19 is explained by a well-balanced immune

3 Cross-Talk between Renin-Angiotensin System (RAS) Dysregulation and Cytokine Storm in COVID-19

SARS-CoV-2 infection is triggered by binding to the ACE2, which is highly expressed in the nasopharynx and lungs, as well as in the cardiovascular system and the gastrointestinal and genitourinary tracts [49]. Although respiratory symptoms usually dominate the clinical presentation of COVID-19, SARS-CoV-2 infection could also be responsible for a variety of potentially serious multiorgan manifestations. ACE2 represents a key enzyme for regulating the RAS that degrades Ang II to Ang-(1–7), mitigating its effects on vasoconstriction, sodium retention, and fibrosis [49]. After the initial involvement of ACE2 by the spike-protein SARS-CoV-2, there is a subsequent downregulation of ACE2, leading to a reduction in Ang-(1–7) [49], which causes an acute lung injury. Importantly, this lesion can be mitigated in animal models by blocking the renin-angiotensin pathway with ACEIs or ARBs [50].

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Further, ACE2 expression in the lungs has been reported to increase with age [57], and, finally, the proportion of fat mass also increases with age [58]. Thus, geriatric patients might also be at greater risk of a cytokine storm if their body mass index does not fall within the obesity range. Indeed, adipose tissue has a proinflammatory effect and Ang II partly mediates it [59].

5 Conclusions

We have recently hypothesized that early administration of sacubitril/valsartan may have a favorable effect on COVID-19 patients [60] by inhibiting neprilysin and RAAS.

Valsartan will continue to block excessive angiotensin-mediated AT1R activation due to the viral infection, and,
in parallel, will upregulate ACE2, thus increasing Ang-
(1–7) production.

Sacubitril/valsartan reduced the concentration of proin-
flammatory cytokines and neutrophil count, while increasing
lymphocyte count more than valsartan alone or placebo [61].

In ill patients, such as patients with acute heart failure,
sacubitril/valsartan was able to mitigate the inflammatory
response and increase the relative lymphocyte count [62].

Steady progress is being made in the treatment of
patients hospitalized for COVID-19. The advances come
with the understanding that the disease is far more
complex than a simple pneumonia. In the early stages of
the disease, modulation of the inflammatory response
through the inhibition of neprilysin and modulation of the
RAAS could modify the course and outcome of the SARS-
CoV-2 infection (Fig. 1). This theoretical assumption
seems worthy of testing not only in heart failure patients
with a recognized indication to sacubitril/valsartan, but
also in broader populations, for instance in hypertensive
patients affected by COVID-19. However, due to the dys-
regulated immune response, geriatric patients qualify as
the optimal target of interventions with the aim of mitigat-
ing the inflammatory response. This would verify whether,
at least in selected populations, sacubitril/valsartan may
qualify as a further aid against COVID-19.

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