

## COVID-19 revolution: a new challenge for the internist

## Renin-angiotensin-aldosterone system in patients with COVID-19

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## ABSTRACT

As the main title '*COVID-19 revolution: a new challenge for the internist*' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, etc.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with renin-angiotensin-aldosterone system in patients with COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus infection disease 2019 (COVID-19), can infect host cells through interaction with membrane-bound angiotensin-converting enzyme 2 (ACE-2) on the respiratory epithelium.<sup>1</sup>

Human ACE-2 is a transmembrane carboxypeptidase comprising a heavily glycosylated N-terminal ectodomain containing the enzymatic active site, a hydrophobic transmembrane domain, and a short intracellular C-terminal tail.<sup>2,3</sup> ACE-2 is found ubiquitously in humans and expressed predominantly in the heart, intestine, kidney, and pulmonary alveolar (type II) cells. The entry of SARS-CoV-2 into human cells is facilitated by the interaction of a receptor-binding domain in its viral spike glycoprotein ectodomain with the ACE-2 receptor.

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ACE-2 belongs to the family of angiotensin-converting enzymes, which are essential regulators of blood pressure, cardiac function, and fluid balance. ACE-2 takes part in the renin-angiotensin-aldosterone system (RAAS), which is an elegant cascade of vasoactive peptides that orchestrate key processes in human physiology.

Angiotensinogen is mainly released by the liver, and it is cleaved by renin, which is secreted by the juxtaglomerular cells in the kidney, thus generating the decapeptide angiotensin I (Ang I). Ang I is converted into angiotensin II (Ang II) by ACE, expressed by the endothelial cells of several organs, such as lung, heart, kidney, and brain. Ang II is the most relevant molecule

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of the RAAS pathway and performs its function by activating the following G-protein-coupled receptors: angiotensin II receptor type 1 (AT1R) and angiotensin II receptor type 2 (AT2R). AT1R induces detrimental effects, such as inflammation, fibrosis, and altered redox balance in addition to vasoconstrictive properties, whereas AT2R is involved in protective and regenerating actions (anti-inflammatory, antifibrotic, neurodegenerative, metabolic) and in the release of vasodilatory molecules.<sup>4-11</sup> Therefore, the equilibrium point of the RAAS is represented by Ang II, which can also be converted into heptapeptide Ang-(1-7) by the action of angiotensin-converting enzyme 2 (ACE2). Ang-(1-9), which can also be generated by the cleavage of ANG I by endopeptidases, binds Mas receptors,<sup>2</sup> counteracting most of the deleterious actions of the ACE/Ang II/AT1 axis, especially in pathological conditions.

ACE-2 is counterregulatory to the activity of angiotensin II generated through ACE-1 and is protective against detrimental activation of the renin-angiotensin-aldosterone system. ACE-2 catalyzes angiotensin II to angiotensin-(1-9), which exerts vasodilatory, anti-inflammatory, antifibrotic, and antigrowth effects.<sup>2</sup>

In clinical studies, serum Ang II levels showed to be significantly elevated in patients with acute lung injury,<sup>5</sup> while high serum Ang II levels have been associated with the severity and mortality of the SARS-CoV-2 infection.<sup>6</sup>

SARS-CoV-2 infects endothelial cells, and that loss of endothelial ACE-2 as a consequence of coronavirus infection confers a pro-inflammatory, procoagulant pro-apoptotic phenotype to endothelial cells.

So, on the one hand, it has been suggested that ACE inhibitors and angiotensin receptor blockers (ARBs) may increase the expression of ACE-2 and thereby may confer a predisposition to more severe infection and adverse outcomes during COVID-19. On the other hand it has been suggested that ACE inhibitors may counter the anti-inflammatory effects of ACE-2.

Starting from these considerations, some have proposed to stop giving ACE inhibitors to patients with COVID-19.

Coexisting conditions, including hypertension, have consistently been reported to be more common among patients with COVID-19 who have had a severe illness, been admitted to the intensive care unit, received mechanical ventilation, or died than among patients who have had a mild illness.

In Italy, the prevalence of hypertension in patients with COVID-19 was 67.6% on the 3<sup>rd</sup> of June according to data from the Italian National Institute of Health (ISS).<sup>7</sup>

The questions remain two: first, is this high prevalence due to the extensive use of ACE-inhibitors provoking an increase of the ACE-2, permitting the virus to enter our organism? Second, is the use of ACE-in-

hibitors harmful for the patient with COVID-19?

Despite these theoretical uncertainties regarding whether pharmacologic regulation of ACE-2 may influence the infectivity of SARS-CoV-2, there is clear potential for harm related to the withdrawal of RAAS inhibitors in patients in otherwise stable conditions. COVID-19 is particularly severe in patients with underlying cardiovascular diseases, and in many of these patients, active myocardial injury, myocardial stress, and cardiomyopathy develop during illness. RAAS inhibitors have established benefits in protecting the kidney and myocardium, and their withdrawal may risk clinical decompensation in high-risk patients.<sup>8</sup> We do not have certainties, but recently two extensive studies faced these problems. Mancina *et al.*<sup>9</sup> conducted a case-control study involving patients with confirmed COVID-19 in the Lombardy region of Italy, which has been severely affected by the pandemic. Neither ACE inhibitors nor ARBs were associated with the likelihood of SARS-CoV-2 infection. An additional analysis comparing patients with severe or fatal infections with matched controls did not show an association between these drugs and severe COVID-19. Reynolds *et al.*<sup>10</sup> conducted a study based on data from the electronic health records of 12,594 patients in the New York University (NYU) Langone Health system tested for COVID-19 between the 1<sup>st</sup> of March and the 15<sup>th</sup> of April, 2020. The investigators' Bayesian analysis showed no positive association for any of the analyzed drug classes, including ACE inhibitors and ARBs, for either a positive test result or severe illness.

Both these studies have weaknesses inherent in observational data, but several other smaller studies from China and the United Kingdom have come to the same conclusion. The American College of Cardiology and the European Society of Cardiology and experts have spoken with one voice in advising that patients should not discontinue ACE inhibitor or ARB therapy out of a concern that they are at increased risk of infection, severe illness, or death during the COVID-19 pandemic.<sup>1</sup> Data from these two studies support those recommendations.

In conclusion, we already know that risk factors for vascular complications include pre-existing vascular morbidities, evidence of high-level systemic inflammation, and perhaps a high viral load. Reducing the viral load and consequently reduce the potential for endothelial cell infection could be of paramount importance.

To infect cells, SARS-CoV-2 binds to the cell surface ACE-2 receptors, and in so doing, compromises the vaso-protective functions of ACE-2, an enzyme that attenuates the vasoconstrictive, pro-inflammatory, pro-apoptotic, prothrombotic and mitogenic effects of angiotensin II.

Angiotensin II-induced experimental hypertension is accompanied by increased thrombosis in large arteries,<sup>11</sup> arterioles,<sup>12</sup> and other blood vessels.<sup>13,14</sup> Thrombosis is a major complication of hypertension, which can be explained by several factors, including alterations in platelets, hypertension-related stress of cell components of the vessel wall, coagulation, and fibrinolysis that promote a pro-thrombotic state.<sup>15,16</sup> Angiotensin II has been implicated as a mediator of thrombosis associated with hypertension, in part because patients treated with ACE inhibitors and angiotensin II receptor blockers have shown a lower incidence of stroke and thrombotic events compared to patients treated with other antihypertensive drugs.<sup>17,18</sup>

Additionally, ACE inhibitors and angiotensin II receptor blockers corrected platelet,<sup>16</sup> coagulation,<sup>19</sup> and fibrinolytic<sup>20</sup> defects. However, the mechanisms responsible for the angiotensin II-dependent activation of the coagulation cascade in large arteries and microvasculature are incompletely understood, having been variously linked to increased plasminogen activator-1 levels, activation of type1 (AT1), type 2 (AT2), type 4 (AT4) angiotensin II receptors, and signaling from receptors for endothelin-1 and bradykinin.<sup>12</sup> A direct role of ACE-2 in reducing thrombosis is supported by experimental results in mice, which showed that XNT, a small molecule ACE-2 activator,<sup>21</sup> reduced platelet attachment to injured endothelium and the size of thrombi, and delayed complete vessel occlusion in mice.<sup>22</sup> Besides, in a model of pulmonary hypertension, angiotensin 1-7, the catalytic product of ACE-2, reduced thrombus formation in hypertensive rats.<sup>23</sup>

Recombinant human ACE-2, the cell entry receptor of SARS-CoV-2, has been shown to competitively neutralize SARS-CoV-2 infection of cells, including endothelial cells *in vitro*. Currently, recombinant human ACE-2 is being tested in initial safety trials, but in a recent review on vasculopathy and coagulopathy associated with SARS-CoV-2 infection, no antithrombotic activity has been reported.<sup>23,24</sup>

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