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CORRESPONDENCE

Downregulation of ACE2 induces overstimulation of the renin–angiotensin system in COVID-19: should we block the renin–angiotensin system?

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Severe acute respiratory syndrome coronavirus 2 is the cause of the ongoing coronavirus disease-19 (COVID-19) pandemic. Mortality is mainly due to acute respiratory distress syndrome (ARDS) [1].

High blood pressure appeared to be an independent factor for severity in patients with COVID-19 [2, 3].

The renin–angiotensin system (RAS) is a hemodynamic and biological system that regulates blood pressure, plasma potassium, and the stability of pulmonary epithelial membranes (Fig. 1) [4]. In this system, two antagonistic pathways are balanced. The first is the angiotensinogen pathway that transforms angiotensinogen into angiotensin I (by renin), and then converts it into angiotensin II by angiotensin converting enzyme (ACE). Angiotensin II attaches to angiotensin II type 1 receptor (AT1R) and activates the system to induce vasoconstriction, aldosterone secretion stimulation, hypokalemia, and pulmonary epithelium degradation [5].

The second way in which the angiotensin system is balanced involves a second angiotensin converting enzyme (ACE2) [6, 7]. This pathway transforms a part of angiotensin I [1–10] and angiotensin II [1–8] before it attaches to its AT1R receptor. The angiotensin I and II phosphorylation products are angiotensin 1–9 and angiotensin 1–7. They attach to the angiotensin II type 2 receptor receiver, inducing antagonist effects compared with AT1R [8].

In the infection phase (Fig. 2), COVID-19 virus uses the enzymatic receptor of ACE2 to penetrate the host cell [9, 10]. Coronavirus binding with ACE2 has been shown to lead to a downregulation of ACE2 [11], contributing to an increase in angiotensin 2 through ACE, as the decrease in ACE2 results in a lower conversion of angiotensin to angiotensin 1–7 vasodilator [12]. The lower the level of ACE2, the lesser angiotensin I [1–10] and angiotensin II [1–8] will be degraded; thus, their plasmatic concentration gradually increases. A US intensive care unit team demonstrated that an increase in angiotensin 1–10 and a decrease in angiotensin 1–9 (its ACE2 processing product) were correlated with a poor prognosis in ARDS [1].

Thus, elevations in angiotensin II concentrations and stimulation of AT1R lead to a decrease in the stability of the pulmonary endothelium and an aggravation of respiratory distress [13, 14]. The other effects are an increased secretion of aldosterone, hypokalemia induced by kaliuresis, and increased sodium reabsorption and inflammation [15].

Hypokalemia is frequently found in patients with COVID-19. A Chinese team recently reported that hypokalemia was associated with a poor outcome (Wuhan's experience) [16].

Conversely, RAS blockers can increase ACE2 and potentially promote virus loading into the cell [17].

We believe that major imbalance in RAS induced by the downregulation of ACE2 is an essential element of unfavorable evolution in patients with COVID-19. The biological marker of this imbalance appears to be hypokalemia.

Several studies in influenza and Ebola lung infections have shown the beneficial role of AT1R blockers on lung damage, with a decrease in inflammation and cytokines [18–21]. In two animal studies, losartan demonstrated an increase in ACE2 expression [22, 23].

Losartan was also the molecule chosen in two trials recently started in the United States by the University of Minnesota to treat patients with COVID-19 (clinical trials.gov NCT04311177 and NCT 104312009). We began a preliminary study to document the kinetics of RAS in COVID+ patients (SAR-COV) before therapeutic evaluation (ISRA-COV).

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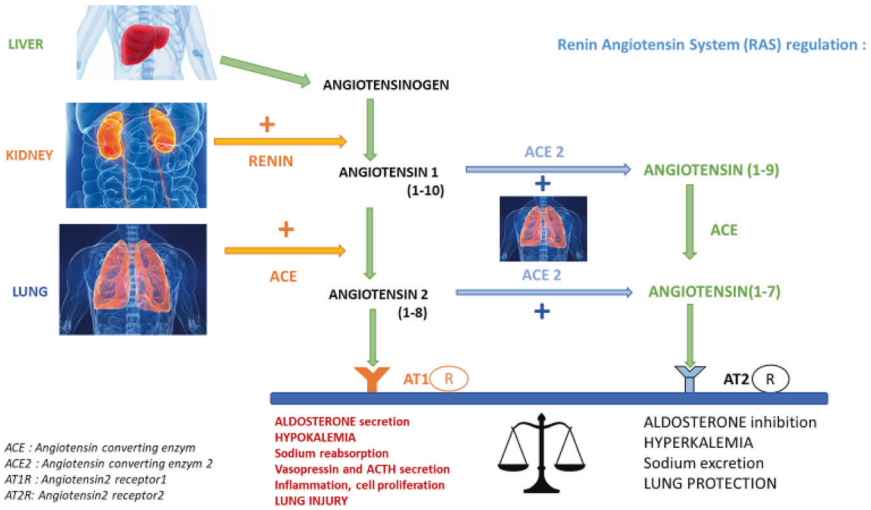

Fig. 1 Renin–angiotensin system (RAS) regulation

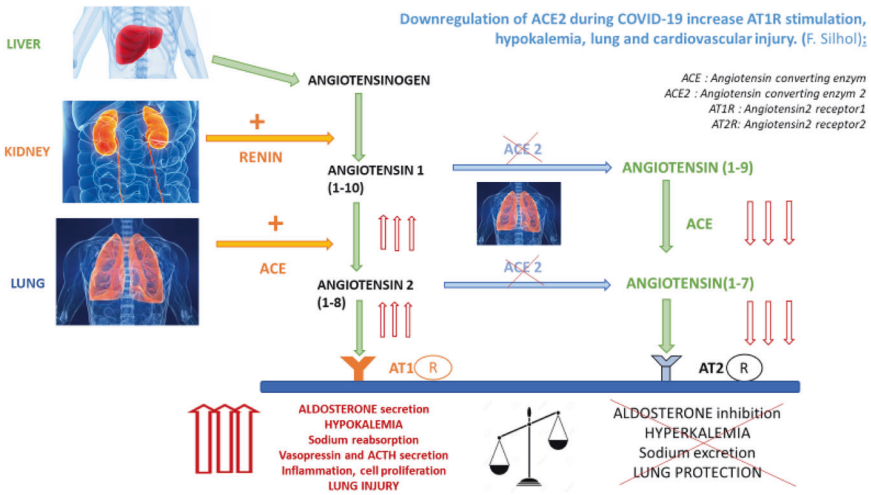

Fig. 2 Downregulation of ACE2 during COVID-19 increases AT1R stimulation, hypokalemia, and lung and cardiovascular injury (FS)

Clarification is needed to determine whether blockers of the angiotensin system have a protective or harmful effect in these patients [24]. In particular, we strongly need to evaluate how blocking the overactivation of the RAS by an AT1R blocker (such as losartan) in patients with COVID-19 could decrease respiratory decompensation and hemodynamic disorders and thus limit the number of patients with poor prognosis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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