Severity of COVID-19: The importance of being hypertensive

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The novel respiratory Syndrome Coronavirus-2 (SARS-CoV-2) caused a cluster of pneumonia cases in China at the end of 2019. After few months, it led to a pandemic that has spread throughout most countries of the world (https://coronavirus.jhu.edu/map.html).

SARS-CoV-2 disease (COVID-19) primarily manifests as a lung infection and its clinical course is characterized by respiratory symptoms ranging from a mild respiratory infection (including fever, cough and fatigue) to pneumonia, acute respiratory distress syndrome (ARDS), shock, and death [1]. Among the proposed mechanisms of injury caused by SARS-CoV-2, there is a "cytokine storm" triggered by an imbalanced response by type 1 and type 2 T helper cells [2]. Furthermore, an emerging body of evidence suggests that COVID-19 may predispose patients to arterial and venous thrombotic disease [3]. Fibrin deposits are found in the lungs possibly due to the dysregulation of the coagulation and fibrinolytic systems: tissue factor is exposed on damaged alveolar endothelial cells promoting fibrin deposition, while significantly elevated levels of plasminogen activator inhibitor 1 (PAI-1) from lung epithelium and endothelial cells create a hypofibrinolytic state [3].

Numerous clinical studies showed that COVID-19 disproportionately affects patients with pre-existing comorbidities. According to a meta-analysis of 7 studies including 1576 laboratory-confirmed COVID-19 infected patients, the most prevalent comorbidity was hypertension [4]. Furthermore, patients with hypertension appear to be at increased risk from COVID-19 infection. More specifically, a pooled analysis of 13 studies, with a total of 2893 patients with COVID-19 documented that hypertension was associated with a 2.5-fold increased risk of severe COVID-19 (odds ratio [OR]: 2.49; 95% confidence interval [CI]: 1.98-3.12; $I^2 = 24\%$) and a higher risk of mortality (OR: 2.42; 95% CI: 1.51-3.90; $I^2 = 0\%$) [5].

Taken together, these findings suggest that hypertension is linked to the pathogenesis of COVID-19. In this regard, the renin-angiotensin-aldosterone-system (RAAS) plays an important role in the pathogenesis of hypertension and the pathways involved in the generation of angiotensin II (Ang II) and Angiotensin$_{1,7}$ (Ang$_{1,7}$) have been recently recognized as potential markers of COVID-19 severity. Angiotensin converting enzyme-2 (ACE_2) receptors are involved in the degradation of Ang II to Ang$_{1,7}$, but they also mediate the entry into the cell of SARS-CoV-2. Of note, Ang$_{1,7}$ opposes the deleterious effects of Ang II, including vasoconstriction, proliferative, profibrofitic and proinflammatory effects, and prothrombotic actions. The entry of SARS-CoV2 into the cells through membrane fusion markedly down-regulates ACE_2 receptors, with loss of the catalytic effect of these receptors at the external site of the membrane. Thus, this phenomenon translates in an increased state of pulmonary inflammation and coagulation (Figure 1).

It has been noted that hypertension may be associated with a variable degree of ACE_2 deficiency [6,7]. In this setting, ACE_2 down-regulation induced by SARS-CoV2 has the potential to be detrimental in hypertensive patients through a further worsening of the unbalance between Ang II and Ang$_{1,7}$ [6,7]. Such dysregulation would markedly decrease the activity of Ang$_{1,7}$, thereby rendering the lungs more susceptible to the detrimental actions of Ang II (Figure 1). In other words, the progression of inflammatory and thrombotic processes may be triggered by Ang II hyperactivity unopposed by Ang$_{1,7}$ [6].

Paraphrasing an aphorism of Oscar Wilde (from "The importance of being Earnest", 1895), we could state that "the truth is rarely pure and never simple". This appears particularly true for the complex mechanisms linking COVID-19 with hypertension. The theorized physiopathological unbalance between Ang II and Ang$_{1,7}$ might play a central role in explaining many clinical features of COVID-19. Notably, it also provides a solid rationale to investigate the impact of some therapeutic measures which include the use of Ang II type 1 receptor blockers, soluble recombinant ACE_2 and Ang$_{1,7}$ [6,7].

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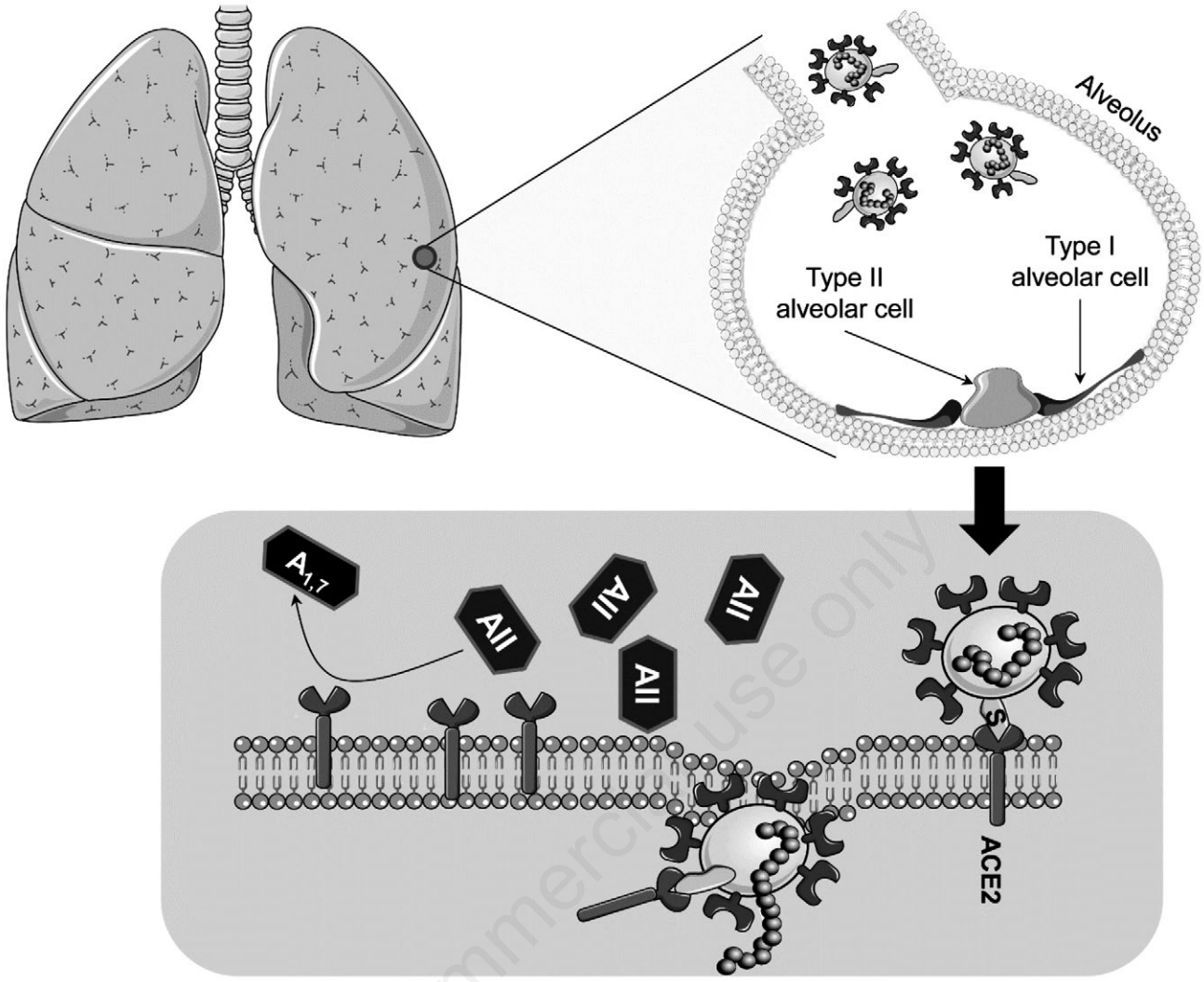

Figure 1. Lung damage during COVID-19. Detrimental effects of ACE_2 down-regulation induced by viral entry in a setting of pre-existing ACE_2 deficiency (see text for details). ACE_2 are mainly expressed in pneumocytes type II, which are responsible for the production of alveolar surfactant, and have the function of 'stem' cells, progenitors of pneumocytes type I (responsible of gas exchanges). AII, angiotensin II; $A_{1,7}$, angiotensin$_{1,7}$; ACE_2, angiotensin converting enzyme-2.

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