Clinical Science (2020) **134** 1259–1264
https://doi.org/10.1042/CS20200492

PORTLAND PRESS

Hypothesis

Covid-19: the renin–angiotensin system imbalance hypothesis

Katharina Lanza*, Lucas G. Perez*, Larissa B. Costa, Thiago M. Cordeiro, Vitria A. Palmeira, Victor T. Ribeiro and Ana Cristina Simões e Silva

Interdisciplinary Laboratory of Medical Investigation, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil

Correspondence: Ana Cristina Simões e Silva (acssilva@hotmail.com)

The emergency of SARS-CoV-2 in China started a novel challenge to the scientific community. As the virus turns pandemic, scientists try to map the cellular mechanisms and pathways of SARS-CoV-2 related to the pathogenesis of Coronavirus Disease 2019 (Covid-19). After transmembrane angiotensin-converting enzyme 2 (ACE2) has been found to be SARS-CoV-2 receptor, we hypothesized an immune-hematological mechanism for Covid-19 based on renin–angiotensin system (RAS) imbalance to explain clinical, laboratory and imaging findings on disease course. We believe that exaggerated activation of ACE/Angiotensin II (Ang II)/Angiotensin Type 1 (AT1) receptor RAS axis in line with reduction of ACE2/Angiotensin-(1-7)/ Mas receptor may exert a pivotal role in the pathogenesis of Covid-19. In this perspective, we discuss potential mechanisms and evidence on this hypothesis.

COVID-19 and ACE2/Angiotensin-(1-7)/Mas receptor axis

The outbreak of Coronavirus Disease 2019 (Covid-19) as pandemic, on March 11, 2020, prompted the urgent need for a better understanding of the disease's pathophysiological mechanisms. The interactions of SARS-CoV-2 in the condition represent an essential knowledge for treatment development and better clinical management of critical patients. Despite angiotensin-converting enzyme 2 (ACE2) being acknowledge as viral receptor early in the pandemic, the suggested pathophysiological mechanisms for Covid-19 do not conceive the renin–angiotensin system (RAS) as a major regulator of disease-related events. The RAS was considered, until early in the 21st century, a single-armed system centered on the Angiotensin II activity as a vasoactive peptide responsible for blood pressure and body fluid homeostasis. The further discovery of the physiological functions of ACE2 and its main product, Angiotensin-(1-7) [Ang-(1-7)] changed the conception of the RAS. In this sense, the RAS is nowadays comprehended as formed by two opposite counter-regulatory arms: the classical one, composed by ACE/Angiotensin II (Ang II)/AT1 receptor (AT1R), and the alternative anti-inflammatory arm, comprising ACE2/Ang-(1-7)/Mas Receptor (MasR) [1]. Then, we postulate that ACE2 targeting by SARS-CoV-2 is not just a casual route of infection, but a causal factor of the disease itself: Covid-19 is, at least in part, the consequence of RAS imbalance, due to an exaggerated activation of the classical arm (ACE/Ang II/AT1R), leading to pulmonary injury, hematological alterations, and hyperinflammatory state. Hence, the RAS imbalance hypothesis suggests that RAS pathway disruption is at the center of Covid-19 pathophysiological mechanisms.

Covid-19 clinical spectrum comprises three main phases: early infection, pulmonary involvement and systemic hyperinflammation. Associated symptomatology comprehends characteristic respiratory infection manifestations, including cough, fatigue and shortness of breath, as well as less common systemic symptoms, like headaches, myalgia and arthralgia [2]. Complementary investigation often shows diffuse

*These authors contributed equally to this work.

Received: 24 April 2020
Revised: 19 May 2020
Accepted: 26 May 2020

Version of Record published: 08 June 2020

Clinical Science (2020) **134** 1259–1264
https://doi.org/10.1042/CS20200492

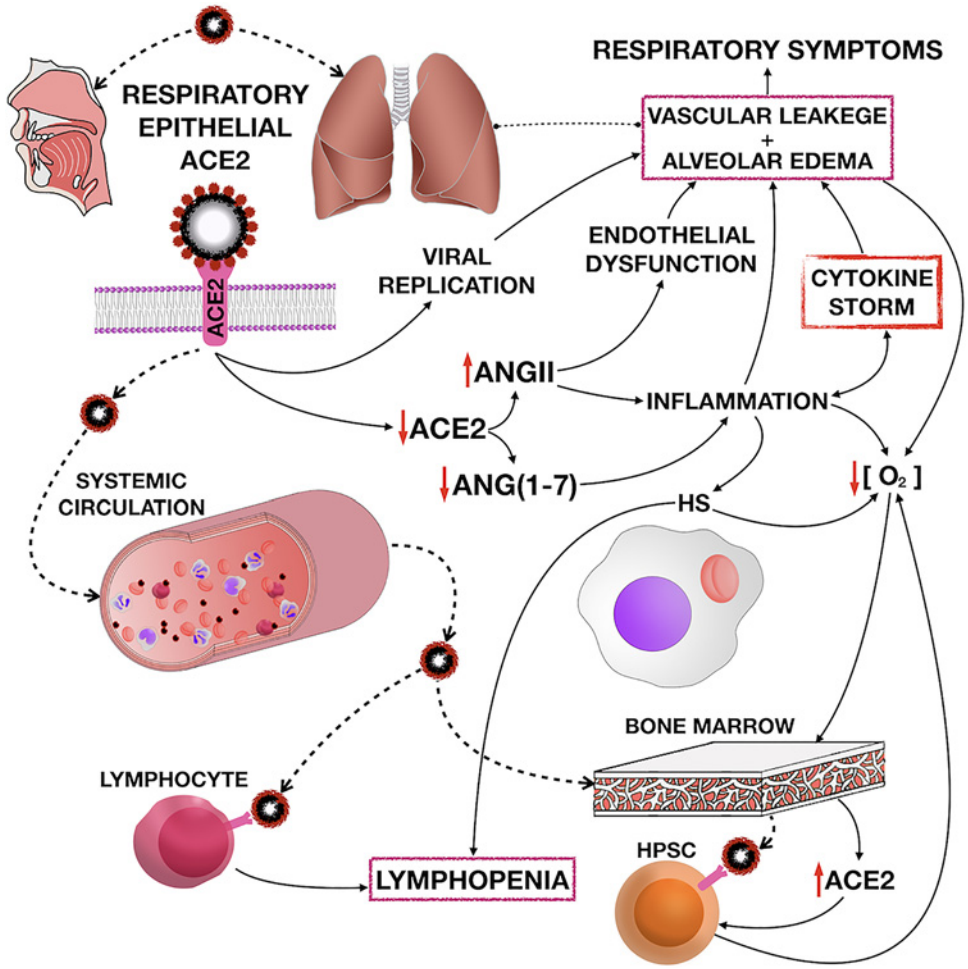

Figure 1. Pathophysiological role of ACE2 in COVID-19

Schematic representation of pathophysiological mechanisms related to COVID-19 and the overlapping pathways with renin–angiotensin system, particularly with the modulation of ACE2. [O2] = Oxygen concentration; HS = Hemophagocytic-like Syndrome; ACE2 = Angiotensin-Converting Enzyme 2; ANG(1-7) = Angiotensin (1-7); ANGII = Angiotensin II; HPSC = Hematopoietic stem/progenitor cell.

ground-glass opacities at computerized tomography and early stage lymphocytopenia, even before dyspnea. Furthermore, epidemiological findings suggest an important association between arterial hypertension and diabetes mellitus and worse disease outcome, therefore composing two very relevant risk factors. On the other hand, patients with coexisting pulmonary disorders, chronic obstructive pulmonary disease, for instance, had less frequently severe presentation, what may seem counter-intuitive. In addition, recent studies have shown a mild disease pattern in the pediatric population, which commonly represents a group more susceptible to respiratory conditions [3]. In light of Covid-19 clinical spectrum phases, we proposed a RAS modulated immune-hematological hypothesis to better comprehend the disease course.

Viral infections initiate with the binding of viral structures to host surface cell receptors. Although several coronaviruses have been described to cause human diseases, only three of them bind to ACE2: SARS-CoV, SARS-CoV-2 and HCoV-NL63 [4]. SARS-CoV was also responsible for a global health emergency, the Severe Acute Respiratory Syndrome (SARS) outbreak that took place in China in 2003. Virus-surface Spike Glycoprotein (S) is the SARS-like coronavirus structure that participates in receptor recognition. Even though a genome similarity between SARS-CoV and the novel coronavirus has been established, several differences in the sequence of amino acid residues in the receptor-binding domain (RBD) of S protein are responsible for differences in affinity. While SARS-CoV has a sharp turn 3 residue motif (Pro-Pro-Ala) in ACE2-binding ridge, SARS-CoV-2 has a 4 residue motif (Gly-Val-Glu-Gly) that forms extra main-chain hydrogen bonds, resulting in a closer contact with N-terminal helix of ACE2 than SARS-CoV

Clinical Science (2020) **134** 1259–1264
https://doi.org/10.1042/CS20200492

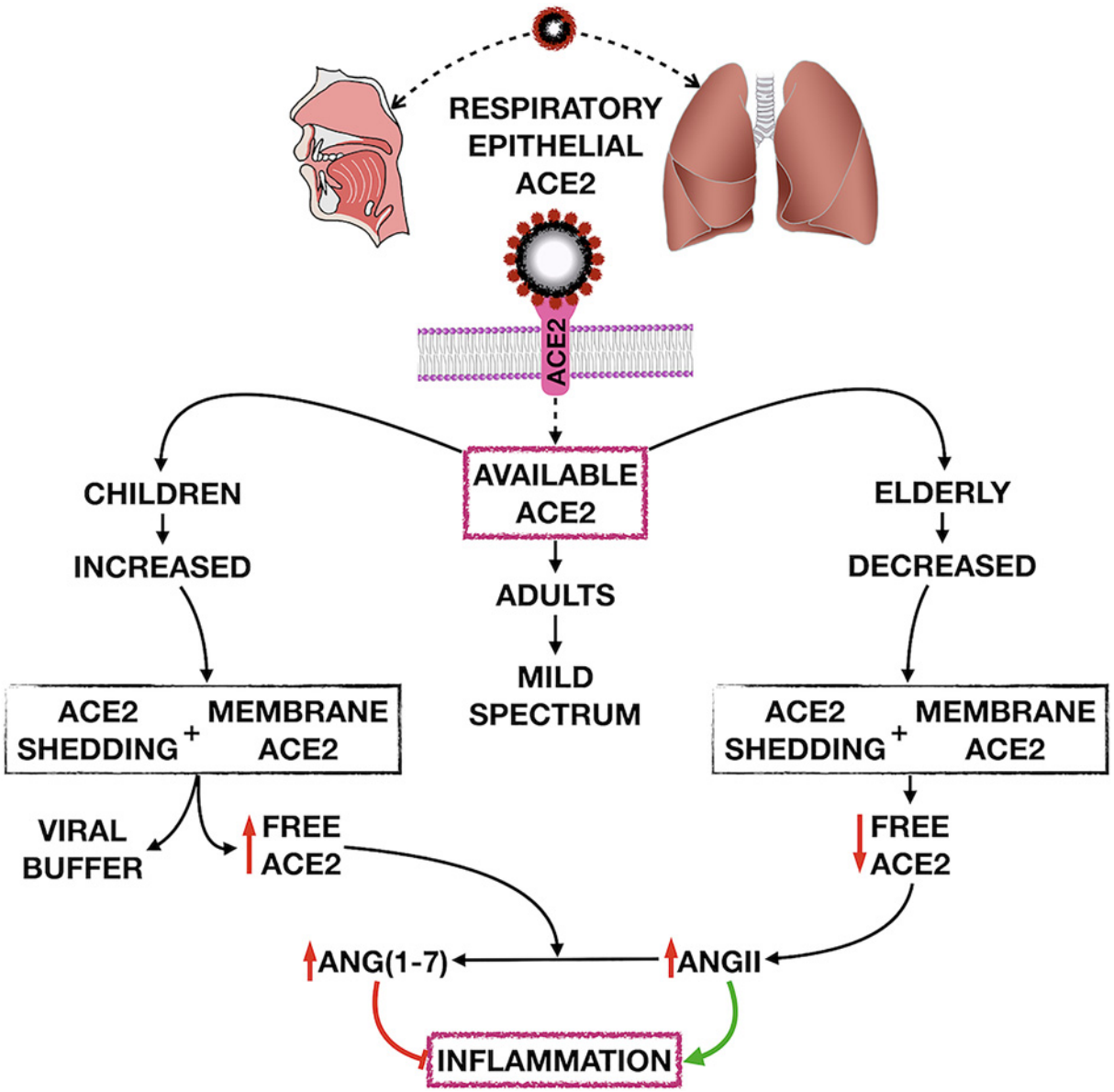

Figure 2. ACE2 basis for age specific differences in COVID-19 outcome

Schematic representation of the differences detected in ACE2 expression according to age. The figure highlights the hypothetical mechanisms related to COVID-19 outcome based on the protective effects of free ACE2 for buffering the viral infection as well as reducing inflammation. ACE2, angiotensin-converting enzyme 2; ANG(1-7), angiotensin (1-7); ANGII, Angiotensin II.

[5]. Furthermore, the presence of Phe486 allows a better insertion into ACE2 hydrophobic pocket. This conformation, added to the higher ability to neutralize receptor's docking hotspots, makes SARS-CoV-2 receptor affinity significantly higher, in comparison with SARS-CoV. The difference between receptor affinities might be an explanation for the greater spread of Covid-19 compared with SARS, but the main pathophysiological mechanism proposed in this article may as well apply to SARS-CoV infection.

The hypothesis of RAS imbalance is mainly based on the reduction of membrane-bound ACE2 as a consequence of enzyme endocytosis complex with the S protein of the virus. ACE2 is largely expressed in the nasal and oropharyngeal epithelium [6], where SARS-CoV-2 entrance occurs. Since the RAS is based on a dynamic equilibrium between two opposite axes, down-regulation of the enzyme responsible for converting Ang II into Ang-(1-7) implicates in enhanced activity of RAS classical axis. Although Ang II is better known for its cardiovascular and renal functions, vasoconstriction and fluid homeostasis for instance, activation of the ACE/Ang II/AT1 axis have been described to

Clinical Science (2020) **134** 1259–1264
https://doi.org/10.1042/CS20200492

deflagrate inflammation, fibrosis, cellular growth and migration [7]. Up-regulation of this classical RAS arm might be partially responsible for the deleterious pathophysiological mechanisms of Covid-19, added by viral activation of the innate and adaptive immune response [8]. The implications of such RAS imbalance for pulmonary manifestations in severe acute distress syndromes were not unnoticed [9]. In this context, experimental mice models of SARS-CoV mediated lung injury had previously shown diminished expression of ACE2 in cell surface, as well as increased Ang II levels in lung tissue after administration of Spike (S318-510)-Fc [10]. Consequently, mice exhibited increased lung edema, neutrophil accumulation and enhanced vascular permeability [10]. Similar findings were obtained in an experimental model of hyperoxic lung injury, in which mice were treated with the ACE2 agonist diminazene aceturate (DIZE), or the ACE2 inhibitor MLN-4760 [11]. Hyperoxia significantly reduced lung ACE2 expression and enzyme activity, leading to an increased Ang II/Ang-(1-7) ratio. In contrast, the administration of DIZE simultaneously to hyperoxia induction significantly enhanced lung ACE2 expression and activity, thus reducing the Ang II/Ang-(1-7) ratio. The treatment with ACE2 inhibitor MLN-4760 in combination to hyperoxia significantly reduced lung ACE2 expression/activity and increased the Ang II/Ang-(1-7) ratio. DIZE attenuated lung injury, inflammatory response and oxidative stress induced by hyperoxia, while MLN-4760 potentiated these mechanisms of pulmonary tissue damage [11]. In line with these experimental findings, we postulated that reduced levels of ACE2 and of Ang-(1-7), due to ACE2 down-regulation exerted by SARS-CoV-2, may as well worsen pulmonary distress in COVID-19, since ACE2 itself and the binding of Ang-(1-7) to MasR can mediate anti-inflammatory, antioxidative and anti-fibrotic effects [7].

Considering the role of ACE2 as the viral receptor and the implication of these interactions, several authors discussed the suspension or continuation of RAS inhibitors therapy after Covid-19 outbreak [12]. Indeed, the administration of angiotensin II receptor antagonists (ARAs) and ACE inhibitors (ACEi) might seem counter-intuitive, since experimental studies pointed to an increased expression of ACE2 after treatment of cardiovascular diseases with these medications in animal models [13], although the extrapolation of this finding to humans deserves further investigation. One might consider that increased expression of transmembrane ACE2, the SARS-CoV-2 receptor, could be interpreted as harmful, due to the possibility of favoring viral entrance [14]. In view of the proposed pathophysiology, the association between SARS-CoV-2 and the bioavailability of ACE2 is rather paradoxical: either (1) the patient has a small ACE2 reservoir and suffers the consequences of the exacerbated pro-inflammatory classical axis or (2) the individual infected has enough ACE2 to resist its depletion and to activate the alternative RAS axis, despite facilitating viral entrance. This conception, added by the understanding of RAS imbalance pivotal role in Covid-19, has turned researchers to consider RAS blockers as potential therapies for the disease. Several clinical trials registered in the National Institutes of Health (NIH) propose low doses of ARAs, as the prototype losartan, for treating the condition (NCT04335123, NCT04312009, NCT04311177). Additionally, as previously mentioned, Ang-(1-7) may exert extra benefits, given its anti-inflammatory and anti-fibrotic effects. In this matter, interventional trials using recombinant human ACE2 (rhACE2) and Ang-(1-7) analogues also seem promising (NCT04287686 and NCT04332666, respectively).

SARS-CoV-2 spreads quickly through the human body, as ACE2 is expressed in a variety of tissues [6]. Hence, hematological manifestations of Covid-19 have called researchers' attention. Lymphopenia is an early disease feature that may be due to direct viral attack to lymphocytes, which expresses ACE2 [15]. In bone marrow, ACE2 is found in hematopoietic stem/progenitor cells (HSPC). Although usually ACE2 expression in this site is small, viral-induced hypoxia has three main consequences: (1) increased proliferation and migration of HSPC; (2) up-regulation of ACE2 and Mas Receptor; and (3) shedding of ACE2 ectodomain in HSPC [16]. Another hypothesis to explain the early lymphopenia and the later hematological manifestations of Covid-19 is the deflagration of the hemophagocytic lymphohistiocytosis (HLH) [17]. Once more, in this case, RAS imbalance plays a pivotal role, as Ang II enhances macrophage activity, while Ang-(1-7) limits it [18]. Hematologic dysfunctions help to explain a striking clinical characteristic of Covid-19 later stages: the presence of severe hypoxia in compliant lungs. However, there may be other explanations for oxygen availability reduction. Potential mechanisms are described by a preprint study on the role of non-structural viral proteins [19]. The infection of HSPC by SARS-CoV-2 triggers an attack against hemoglobin produced in erythrocytes precursors by three main proteins: orf1ab, ORF3a and ORF10. In this sense, HSPC might be capable to capture protoporphyrin-IX and to release iron, rendering hemoglobin useless for future oxygen uptake. Other possible mechanisms of lung damage might be related to the elevation of iron levels by increasing oxidative stress in pneumocytes, and the loss of lung perfusion regulation [20]. Presumably, this would be the result of endothelial dysfunction, which is already enhanced by Ang II. Ang II produces endothelial dysfunction and blunts vascular smooth muscle cells' response to vasodilators [21]. This mechanism would be worsened due to the reduction of local protection elicited by Ang-(1-7). Again, RAS imbalance critically affects homeostatic mechanisms.

Advanced and severe forms of Covid-19 are associated with cytokine storm syndrome (CSS), which pathophysiological mechanisms might be explained by several pathways. The first mechanism considers the down-regulation of

ACE2 and consequent increased of Ang II, as this molecule is not converted into Ang-(1-7). Consequently, the uncontrolled stimulation of the ACE/Ang II/AT1R axis results in increased pro-inflammatory cytokines, including IL-1, IL-6 and TNF-α, intensified by the activation of innate and adaptive immune [22]. The virus is also able to enhance DNA-binding activity of nuclear factors, such as NF-KB, which may increase mRNA transcription of several interleukins. Another potential mechanism of injury is a direct consequence of rapid virus replication in lung epithelial and endothelial cells. Pulmonary microvascular and alveolar damage with increased cell apoptosis potentiate even more inflammatory response [23] and compromise the alveolar endothelial cell barrier. All these pathophysiological changes together result in vascular leakage and alveolar edema, both responsible for hypoxia and dyspnea [24]. Because of the key role played by the immune response to Covid-19 infection, several interventional trials registered in NIH aim to evaluate the effects of immune modulation therapy in infected patients. Drugs mainly used in these clinical trials include Tocilizumab, Baritinib and the antimalarial medication Hydroxychloroquine, which also exert an immunomodulatory role [25]. Figure 1 shows potential pathophysiological mechanisms related to SARS-CoV-2 infection, emphasizing the pivotal role of RAS.

RAS imbalance hypothesis also explains the Covid-19 epidemiological pattern. Due to ACE/Ang II/AT1R axis activation in parallel with ACE2/Ang-(1-7)/MasR axis down-regulation in the elderly, hypertensive, diabetic and cardiovascularly compromised patients, mortality rates of these groups are considerably elevated [26]. In addition, several epidemiological data showed a significant male predominance in all age groups [27]. On that matter, Xudong et al. (2004) showed an important reduction in the expression of ACE2 in lungs of rats throughout the aging process. [28]. In advanced age animals, male rats had even more reduced ACE2 levels in comparison with female animals. Additionally, the same experimental study showed higher levels of ACE2 in younger rats [28]. This experimental finding might be one of the reasons to explain why pediatric patients with Covid-19 generally have lower frequency of disease and less severity and fatality case rates in comparison with adults [29]. Furthermore, AT2 receptor, which physiological actions are comparable to MasR regarding its anti-inflammatory properties, might be another protective factor for pediatric patients, once aging progression diminishes its expression [30]. Combined with the proposed RAS imbalance hypothesis and the previously presented paradox, ARAs and ACEi therapeutic approach might be crucial for the best clinical management of the condition due to the stimulation of RAS alternative axis. In this sense, the lower than expected incidence of Covid-19 in patients on hemodialysis favors the overall hypothesis and treatment option, as (1) patients with chronic kidney disease are commonly treated with ACEi or ARAs; and (2) hemodialysis promotes clearance of viremia and of circulating cytokines. Figure 2 illustrates potential differences in regard to RAS molecules and Covid-19 clinical manifestations according to changes in the expression of RAS molecules and receptors.

Several mechanisms related to Covid-19 pathophysiology are yet to be clarified for total comprehension of disease course. The explanations so far considered different disease manifestations (respiratory, hematological or inflammatory) as isolated phenomena without interactions between each other. We do believe that the RAS imbalance hypothesis embraces all of the stages and clinical findings of SARS-CoV-2 infection, placing RAS molecules at the center of Covid-19 pathophysiology. Imbalance between ACE/Ang II/AT1R and ACE2/Ang-(1-7)/MasR axes results in multiple organ dysfunction and uncontrolled inflammatory response. In light of our hypothesis, therapeutic and preventive strategies should take into account the potential role of medications that inhibit classical RAS axis as well those that trigger alternative RAS axis effects.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

ACE2, angiotensin-converting enzyme 2; Ang II, Angiotensin II; AT1, Angiotensin Type 1; Covid-19, Coronavirus Disease 2019; RAS, RAS.

References

1 Touyz, R., Li, H. and Delles, C. (2020) ACE2 the Janus-faced protein – from cardiovascular protection to severe acute respiratory syndrome-coronavirus and COVID-19. *Clin. Sci.* **134**, 747–750, https://doi.org/10.1042/CS20200363

2 Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J. et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* **382**, 1708–1720, https://doi.org/10.1056/NEJMoa2002032

3 Nair, H., Nokes, D., Gessner, B., Dherani, M., Madhi, S., Singleton, R. et al. (2010) Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet North Am. Ed.* **375**, 1545–1555, https://doi.org/10.1016/S0140-6736(10)60206-1

Clinical Science (2020) **134** 1259–1264
https://doi.org/10.1042/CS20200492

4 Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z. et al. (2020) Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. *Cell* **181**, 894.e9–904.e9, https://doi.org/10.1016/j.cell.2020.03.045
5 Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H. et al. (2020) Structural basis of receptor recognition by SARS-CoV-2. *Nature* **581**, 221–224, https://doi.org/10.1038/s41586-020-2179-y
6 Nehme, A., Cerutti, C., Dhaouadi, N., Gustin, M., Courand, P., Zibara, K. et al. (2015) Atlas of tissue renin-angiotensin-aldosterone system in human: A transcriptomic meta-analysis. *Sci. Rep.* **5**, https://doi.org/10.1038/srep10035
7 Rodrigues Prestes, T., Rocha, N., Miranda, A., Teixeira, A. and Simoes-e-Silva, A. (2017) The Anti-Inflammatory Potential of ACE2/Angiotensin-(1-7)/Mas Receptor Axis: Evidence from Basic and Clinical Research. *Curr. Drug Targets* **18**, https://doi.org/10.2174/1389450117666160727142401
8 Imai, Y., Kuba, K., Rao, S., Huan, Y., Guo, F., Guan, B. et al. (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **436**, 112–116, https://doi.org/10.1038/nature03712
9 Siddiqi, H. and Mehra, M. (2020) COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. *J. Heart Lung Transplant.* **39**, 405–407, https://doi.org/10.1016/j.healun.2020.03.012
10 Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B. et al. (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nat. Med.* **11**, 875–879, https://doi.org/10.1038/nm1267
11 Fang, Y., Gao, F. and Liu, Z. (2019) Angiotensin-converting enzyme 2 attenuates inflammatory response and oxidative stress in hyperoxic lung injury by regulating NF-κB and Nrf2 pathways. *QJM* **112**, 914–924, https://doi.org/10.1093/qjmed/hcz206
12 AlGhatrif, M., Cingolani, O. and Lakatta, E. (2020) The Dilemma of Coronavirus Disease 2019, Aging, and Cardiovascular Disease. *JAMA Cardiol.*, https://doi.org/10.1001/jamacardio.2020.1329
13 Zheng, Y., Ma, Y., Zhang, J. and Xie, X. (2020) Reply to: 'Interaction between RAAS inhibitors and ACE2 in the context of COVID-19. *Nat. Rev. Cardiol.* **17**, 313–314, https://doi.org/10.1038/s41569-020-0369-9
14 Guo, J., Huang, Z., Lin, L. and Lv, J. (2020) Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A Viewpoint on the Potential Influence of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers on Onset and Severity of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J. Am. Heart Assoc.* **9**
15 Wang, X., Xu, W., Hu, G., Xia, S., Sun, Z., Liu, Z. et al. (2020) SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion. *Cell. Mol. Immunol.*, https://doi.org/10.1038/s41423-020-0424-9
16 Joshi, S., Wollenzien, H., Leclerc, E. and Jarajapu, Y. (2019) Hypoxic regulation of angiotensin-converting enzyme 2 and Mas receptor in human CD34 + cells. *J. Cell. Physiol.* **234**, 20420–20431, https://doi.org/10.1002/jcp.28643
17 Mehta, P., McAuley, D., Brown, M., Sanchez, E., Tattersall, R. and Manson, J. (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet North Am. Ed.* **395**, 1033–1034, https://doi.org/10.1016/S0140-6736(20)30628-0
18 Simões e Silva, A., Silveira, K., Ferreira, A. and Teixeira, M. (2013) ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *Br. J. Pharmacol.* **169**, 477–492, https://doi.org/10.1111/bph.12159
19 Wenzhong, l. and Hualan, L. (2020) COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to InhibitHuman Heme Metabolism.
20 Gattinoni, L., Coppola, S., Cressoni, M., Busana, M., Rossi, S. and Chiumello, D. (2020) COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. *Am. J. Respir. Crit. Care Med.* **201**, 1299–1300, https://doi.org/10.1164/rccm.202003-0817LE
21 Sardu, C., Gambardella, J., Morelli, M., Wang, X., Marfella, R. and Santulli, G. (2020) Is COVID-19 an Endothelial Disease? *Clin. Basic Evidence*
22 Tanaka, T., Narazaki, M. and Kishimoto, T. (2014) IL-6 in Inflammation, Immunity, and Disease. *Cold Spring Harb. Perspect. Biol.* **6**, a016295–a016295, https://doi.org/10.1101/cshperspect.a016295
23 Liu, Q., Zhou, Y. and Yang, Z. (2015) The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell. Mol. Immunol* **13**, 3–10
24 Channappanavar, R. and Perlman, S. (2017) Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopathol.* **39**, 529–539, https://doi.org/10.1007/s00281-017-0629-x
25 Sahraei, Z., Shabani, M., Shokouhi, S. and Saffaei, A. (2020) Aminoquinolines against coronavirus disease 2019 (COVID-19): chloroquine or hydroxychloroquine. *Int. J. Antimicrob. Agents* **55**, 105945, https://doi.org/10.1016/j.ijantimicag.2020.105945
26 Nikpouraghdam, M., Jalali Farahani, A., Alishiri, G., Heydari, S., Ebrahimnia, M., Samadinia, H. et al. (2020) Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. *J. Clin. Virol.* **127**, 104378, https://doi.org/10.1016/j.jcv.2020.104378
27 Jin, J., Bai, P., He, W., Wu, F., Liu, X., Han, D. et al. (2020) Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front. Public Health* **8**, https://doi.org/10.3389/fpubh.2020.00152
28 Xudong, X., Junzhu, C., Xingxiang, W., Furong, Z. and Yanrong, L. (2006) Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci.* **78**, 2166–2171, https://doi.org/10.1016/j.lfs.2005.09.038
29 Colafella, K., Hilliard, L. and Denton, K. (2016) Epochs in the depressor/pressor balance of the renin–angiotensin system. *Clin. Sci.* **130**, 761–771, https://doi.org/10.1042/CS20150939
30 Kaschina, E., Namsolleck, P. and Unger, T. (2017) AT2 receptors in cardiovascular and renal diseases. *Pharmacol. Res.* **125**, 39–47, https://doi.org/10.1016/j.phrs.2017.07.008