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ACE/ACE2 balance might be instrumental to explain the certain comorbidities leading to severe COVID-19 cases

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The outbreak of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a global catastrophe. The elderly and people with comorbidity are facing a serious complication of the disease. The entry and infection strategy of SARS-CoV-2 in a host cell is raised by an amazing way of angiotensin-converting enzyme (ACE) 2 (ACE2) receptor recognition and imbalance of ACE/ACE2 in various organs, especially in the lungs. Here it has been discussed the role of interferon and protease during the receptor recognition (beginning of infection) and followed by the impact of cytokine and hypoxia in the context of the balance of ACE/ACE2. It has also very concisely delineated the biochemistry and mechanism of ACE/ACE2 balance in different stages of infection and its role in comorbidity.

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) disease is an emerging global threat. Old age or people with any age who have serious chronic health issues (non-monitored hypertension, heart disease, obesity, diabetes, cancer, immuno-suppression status) are more susceptible to the complication and severity of the disease (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html).

Entry of SARS-CoV-2 and its infection

Interferon stimulation

It has been found that SARS-CoV-2 spike protein (S1) binds to its receptor, angiotensin-converting enzyme (ACE) 2 (ACE2) (Figure 1: 3” and 4”) to enter human lung cells (bronchial ciliated epithelial cell and type II pneumocytes) similar to the action of SARS-CoV [1,2]. Induction of the interferon-stimulated gene (ISG) is significant for the antiviral defense mechanism [3,4]. ACE2 (STAT1-binding sites) has been reported as an ISG in epithelial cells [5]. The fallacy is that, SARS-CoV-2 recognizes ACE2 to enter host cells, so SARS-CoV-2 could utilize the ACE2-mediated tissue-protective response to provide additional cellular entry targets. This scheme employed by SARS-CoV-2 could pose serious threat to the human host [6]. The balanced role of IFN (type I, II and III) in tissue protection and host restriction of SARS-CoV-2 infection is, therefore, significant [5,7].

Host protease and bonding with receptor

Host cell proteases (cathepsin, trypsin factor X, furin and TMPRSS2) impart a major role in the priming of viral spikes and their entry into the cell via receptor binding [7]. Both spike proteins and ACE2
Figure 1. Balance of ACE and ACE2 activity in normal individuals and hypertensive/hyperglycemic persons and in case of infection by SARS-CoV-2

ACE converts Ang I into Ang II (arrow 1 and 2; where thick reddish arrow-(2) indicates the higher activity of ACE in hypertensive/hyperglycemic/CKD, i.e. comorbid patients) and ACE2 converts Ang II into Ang (1-7) (arrow 3 and 4) (thick green arrow demonstrates higher ACE2 activity in normal) and dotted red arrows [3" and 4"] indicate ACE2 activity (impaired activity) after SARS-CoV-2 binding. In normal, ACE activity is counterbalanced by ACE2, i.e. ACE ≈ ACE2; but in diseased state, imbalance of ACE and ACE2 (indicates arrow 7) and furthermore while SARS-CoV-2 binds to ACE2, there is high imbalance of ACE and ACE2 activity, i.e. ACE >> ACE2 because of impairment of ACE2 (arrow 8). When normals are infected by SARS-CoV-2, the balance of ACE and ACE2 shows in arrow 5. Boxes A–D represent the effect of imbalance of ACE and ACE2 activity. And this regulatory mechanism (balance/imbalance) of ACE and ACE2 is global in certain cell types. Turquoise brackets ([ ]) represent related references in the figure.

are proteolytically modified during bonding and entry. The binding affinity of SARS-CoV-2 to ACE2 is stronger than SARS-CoV, with modifications in several amino acid residues [8] that lead to augmented hydrophobic interactions and salt bridge structures [9,10]. This may explain the significantly greater infectivity and spreading ability of COVID-19 than the previously occurring SARS. ADAM-17, a disintegrin and metalloproteinase 17, has a proteolytic effect on ACE2 [11,12]. It was also found that over-activated renin–angiotensin system (RAS) can enhance ACE2 shedding and subsequently the up-regulation of ADAM-17 (increase in ADAM-17 activity due to the ROS-induced phosphorylation [13]) induces heart failure, acute coronary disease due to the loss of ACE2. As such Ang II is accumulated and impairment of conversion of Ang II into Ang (1-7) leads to RAS-mediated pernicious effect in a feedback cycle [14,15]. It could be possible that S1 protein-bound ACE2 receptors may not function properly and that the adverse interaction between SARS-CoV-2 and ACE2 may be more prominent in males due to the androgenic hormone testosterone [16]. Action of this hormone results in the inhibition of Ang (1-7)-induced NO signaling through the angiotensin II type-2 receptor (AT2R) down-regulation [16]; contrarily, estrogen in females may protect this flow of adverse effects [17].
Cytokine induction
Loss of balance between anti-inflammatory and pro-inflammatory cytokines causes chronic and mild inflammation, i.e. ‘inflame aging’ in elderly patients. This is one of the causes of diabetes mellitus [18]. Previously developed ‘inflame aging’ generates ‘cytokine storm’ during SARS-CoV-2 infection by enhanced production of TNF-α, IL-1β and IL-6 [19]. These elevated levels of pro-inflammatory cytokines are attributed to diabetes [18]. These cytokines generate adverse immunological responses during SARS-CoV-2 infection [20].

ACE and ACE2 balance in COVID patients and in normal people
ACE and ACE2 activity
ACE catalyzes the conversion of Ang I into Ang II [21] (Figure 1: 1 and 2); the Ang II is a vasoconstrictor that induces oxidative stress and hypertension [22,23]. On the other hand, ACE activity is counterbalanced by ACE2 which converts Ang II into Ang (1-7) which is a vasodilator (Figure 1: 3,6,B) [24]. In hypertensive or diabetic persons, the hyperactivity of ACE results in more production of Ang II than to the production of Ang (1-7) from Ang II by ACE2. As a result, it persuades endothelial dysfunction, NO inhibition, hypoxia, angina, platelet aggregation [25], myocardial infarction and kidney disorders (Figure 1: 4,7,C) [26].

Comorbidity and SARS-CoV-2
When these comorbid patients are infected with the SARS-CoV-2 by the ACE2 receptor-recognition (Figure 1:4”), they become vulnerable. Because, previously developed abnormal endothelial cells (glycocalyx coat) become the basement of the adhesion and aggregation of large number of platelets [27,28]. In diabetes, the bioavailability of diminished NO coupling with up-regulated NADPH oxidase might be the cause of endothelial dysfunction [29]. On the other hand, it has been found that ACE2/Ang (1-7) has a significant role in the protection of CD34+ or CAC cell (vascular reparative function) dysfunction in diabetes [30]. So, diabetes-induced loss of CAC or CD34+ (vascular reparative cell) may have a role in the creation of vascular dysfunction in COVID patients and as such viral myocarditis, heart failure and cardiac arrest have been found in the patients. [30,31]. In diabetes, dysfunction of RAS is connected to heart failure with preserved ejection fraction (HFpEF) and loss of ACE2 also dampens the HFpEF. ACE2/Ang (1-7) may have significant role in the regulation of cardio-fibroblasts, cardiomyocytes and endothelial cells in case of both HFpEF and heart failure with reduced ejection fraction [32]. The ultimate eventuality is the multiple organ failure and death of the patients [33].

Patients with COPD/ARDS also face severe breathing problems due to acute lung injury (ALI) by chronic hypoxia and drastic NO-level drop (Figure 1:8,D) [34,35]. As such, the production of Ang II is so high due to high ACE activity, ACE2 is unable to counterbalance the production of Ang (1-7) (Figure 1:8). As a consequence, Ang II-induced dampening is higher in the lungs, heart and kidney cells [36,37]. It has been reported in normal individuals that the ACE2–Ang (1-7)–Mas axis imparts in the redox signaling and maintains vascular tone through the NO-induced vasodilatory action (Figure 1:B) [26] and deficiency of ACE2 might up-regulate the endothelial dysfunction and pro-inflammatory stimuli [35]. It is also significant that the oxidative stress induced by Ang II is responsible for the reduction in tetrahydrobiopterin synthesis and the uncoupling of eNOS resulting in a massive drop of endothelial NO level [38]. Vasoclectronstriction occurs in the increasing state of ACE/Ang II [18,19] and it might be possible that ACE/Ang II-induced hypertension may provoke hypertension-end organ damage by suppressing endothelial nitric oxide synthase activity [39]. ACE2-mediated protection of lung injury was also investigated in ace2-knockout mice model [40]. It was also found that immunotargeting via anti-ACE could limit the I/R injury of lungs through the antioxidative defense mechanism of pulmonary endothelium cells [41].

Hypoxia-inducible factor and ACE2
Hypoxia-inducible factor (HIF) 1α (HIF-1α), the master regulator of oxygen homeostasis in the cell plays the crucial role during cardiac development, coronary perfusion and angiogenesis [42]. But with aging and high-risk factors (diabetes, pre-hypertension), the function of HIF-1α may not be restored and as a result, the sustained action of HIF becomes lower in COVID-19 patients, especially who are aged and have comorbid nature (diabetic, hypertensive, COPD). Individuals with HIF polymorphism are also susceptible for this disease [43]. Long-term (chronic) hypoxia-induced HIF may up-regulate ACE and down-regulate ACE2 [44]. In contrast, normal individuals who are infected by SARS-CoV-2, may face less complications than elder and comorbids patients specifically with pneumonia, ARDS, kidney injury etc. [45] and it might be due to the change of HIF level and as a consequence imbalance
regulation of ACE/ACE2 ratio due to the increase in hypoxia, ACE and decrease in ACE2 imparts a major role in hypoxic pulmonary hypertension (HPH) (Figure 1:5,A) [34]. Nevertheless, in a recent study, SARS-CoV-2 infection was found occurring at a lower rate in high altitudes (>2500 m) possibly due to physiological acclimatization to hypoxia with higher HIF level and down-regulation of ACE-2 [46]. In hypoxia, the cell adapts under stress condition and HIF-1α induces the expression of pyruvate dehydrogenase kinase-1 (PDK1) which inhibits the pyruvate dehydrogenase (PDH), so pyruvate entry into TCA cycle is inhibited, as a consequence glucose metabolism shunts to glycolysis [47,48]. Thus, HIF-1α might have a fine-tuning on optimization of glucose and O2 utilization in hypoxic condition to produce enough energy without generating ROS through the inhibition of mitochondrial respiration [48]. The HIF-1α may play a pivotal role in chronic kidney disease by producing erythropoiesis in hypoxic conditions. Thus, the inhibition HIF-1α-hydroxylase could be a supportive therapy in sudden onset of the hypoxic condition in COVID-19 patients through the cellular adaptation [49].

**ACE and Ang II receptor blockers in COVID-19**

It is reported that, ACE blockers, Ang II receptor blockers (ARBs) are supportive therapy to inhibit the Ang II-induced hypertension, kidney function and lung congestion, but these are not direct therapy against viral infection. Rather, these drugs only control the comorbid symptoms in the COVID-19 patients [50]. Few contrasting reports are also there, these ARB or ACEI augment the severity in some of the COVID patients [51]. However, it may be hypothesized that ACEI or ARB should not be withheld from the high-risk AMI, heart failure, CVD and hypertensive patients according to the statement of American Heart Association [52,53]. The targeting RAS-axes might be a way to recuperate clinical outcome of COVID patients by using ARB [15] (Figure 1:E).

**Conclusion**

From the above discussion, it can be delineated that ACE2 is involved from the step of entry-infection strategy of SARS-CoV-2 to its adverse life-threatening effect in host cell (heart, lungs, kidney), so ACE/ACE2 has undoubtedly significant role in disease progression and prognosis in humans. The RAS, therefore, plays a crucial role in SARS pathogenesis and ACE2 could be a way to block the spread of SARS-CoV. ACE2 was found to be an effective therapy to control lung injury and it was also investigated in Ace2-knockout murine lungs [40] and further, it has been found that immunotargeting via anti-ACE could protect lungs [41]. As a result, modulation of the RAS by the balancing of ACE and ACE2 might be one of the ways to attenuate the ALI in SARS-CoV and its complicity [35] and ACE2-Ang (1-7) axis could be a potent therapeutic window for the prevention of heart failure [32].

**Data Availability**

This submission cannot comply with the data type-specific deposit requirements.

**Competing Interests**

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

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**Author Contribution**

Sarbashri Bank: designed, conceptualized and wrote the whole manuscript. Subrata Kumar De, Smarajit Maiti and Madhusudan Das: provided intellectual input and helped in critical thinking in manuscript. Biswabandhu Bankura and Gausal Khan: provided input in write-up. Each author reviewed the manuscript.

**Ethics Approval**

This article does not contain any studies with human participants or animals performed by any of the authors.

**Abbreviations**

ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitors; ACE2, angiotensin-converting enzyme-2; ADAM-17, a disintegrin and metalloproteinase 17; ALI, acute lung injury; AMI, acute myocardial infarction; Ang II, angiotensin II; ARB, Ang II receptor blocker; ARDS, acute respiratory distress syndrome; CAC, circulating angiogenic cell; COPD, chronic obstructive pulmonary disease; eNOS, endothelial nitric oxide synthase; HFpEF, heart failure with preserved ejection fraction;
HIF, hypoxia-inducible factor; I/R, ischemia/reperfusion; ISG, interferon-stimulated gene; RAS, renin–angiotensin system; S1, spike protein; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; TMRPSS2, Transmembrane protease serine 2.

References

1. Li, W., Moore, M.J., Vasilieva, N., Sui, J., Wong, S.K., Berne, M.A. et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426, 450–454, https://doi.org/10.1038/nature02145
2. Qian, Z., Travanty, E.A., Oko, L., Edeen, K., Berglund, A., Wang, J. et al. (2013) Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome coronavirus. Am. J. Respir. Cell Mol. Biol. 48, 742–748, https://doi.org/10.1165/rcmb.2012-0339OC
3. Deeks, S.G., Odorizzi, P.M. and Sekaly, R.P. (2017) The interferon paradox: can inhibiting an antiviral mechanism advance an HIV cure? J. Clin. Invest. 127, 103–105, https://doi.org/10.1172/JCI91916
4. Bailey, C.C., Zhong, G., Huang, I.C. and Farzan, M. (2014) IFITM-family proteins: the cell’s first line of antiviral defense. Annu. Rev. Virol. 1, 261–283, https://doi.org/10.1146/annurev-virology-031414-085537
5. Broggi, A., Granucci, F. and Zanoni, I. (2020) Type III interferons: balancing tissue tolerance and resistance to pathogen invasion. J. Exp. Med. 217, e20190295, https://doi.org/10.1084/jem.20190295
6. Zhao, X., Guo, F., Liu, F., Cuconati, A., Chang, J., Block, T.M. et al. (2014) Interferon induction of IFITM proteins promotes infection by human coronavirus OC43. Proc. Natl. Acad. Sci. U.S.A. 111, 6765–6761, https://doi.org/10.1073/pnas.1320856111
7. Ziegler, C.G.K. et al. (2020) SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell 1016–1035, https://doi.org/10.1016/j.cell.2020.04.035
8. Wu, A., Peng, Y., Huang, B., Ding, X., Wang, X., Niu, P. et al. (2020) Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 27, 325–328, https://doi.org/10.1016/j.chom.2020.02.001
9. WANG, J., Ye, G., Shi, K. 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
10. Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y. and Zou, Q. (2020) Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 367, 1444–1448, https://doi.org/10.1126/science.aabb2762
11. Black, R.A., Rauch, C.T., Koslowsky, C.J., Peschon, J.J., Slack, J.L., Wolfson, M.F. et al. (1997) A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385, 729–733, https://doi.org/10.1038/385729a0
12. Patel, V.B., Clarke, N., Wang, Z., Fan, D., Parajuli, N., Basu, R. et al. (2014) Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. J. Mol. Cell Cardiol. 66, 167–176, https://doi.org/10.1016/j.yjmcc.2013.11.017
13. Scott, A.J., O’Dea, K.P., O’Callaghan, D., Williams, L., Dokpesi, J.O., Tatton, L. et al. (2011) Reactive oxygen species and p38 mitogen-activated protein kinase mediate tumor necrosis factor α-converting enzyme (TACE/ADAM-17) activation in primary human monocytes. J. Biol. Chem. 286, 35466–35476, https://doi.org/10.1074/jbc.M111.277434
14. Xu, J. et al. (2017) Clinical relevance and role of neuronal AT1 receptors in ADAM17-mediated ACE2 shedding in neurogenic hypertension. Circ. Res. 121, 43–55, https://doi.org/10.1161/CIRCRESAHA.116.310509
15. Gheblawi, M. et al. (2020) Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ. Res. 126, 1456–1474, https://doi.org/10.1161/CIRCRESAHA.120.317015
16. Mishra, J.S., Hanksin, G.D. and Kumar, S. (2016) Testosterone downregulates angiotensin II type-2 receptor via androgen receptor-mediated ERK1/2 MAP kinase pathway in rat aorta. J. Renin Angiotensin Aldosterone Syst. 17, 147032016674875, https://doi.org/10.1177/147032016674875
17. Steglich, K.E., Canepa-Escaro, F., Schiiliro, M., Berndnikovs, S., Prakash, Y.S. and Chiarella, S.E. (2020) Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. Am. J. Physiol. Lung Cell. Mol. Physiol. 318, L1280–L1281, https://doi.org/10.1152/ajplung.00153.2020
18. Mirza, S., Dossain, M., Mathews, C. et al. (2012) Type 2 diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: a cross-sectional study. Cytokine 57, 136–142, https://doi.org/10.1016/j.cyto.2011.09.029
19. Meftahi, G.H., Jangravi, Z., Sahraei, H. et al. (2020) The possible pathophysiology mechanism of cytokine storm in elderly adults with COVID-19 infection: the contribution of “inflammaging”. Inflamm. Res. 69, 825–839, https://doi.org/10.1007/s00011-020-01372-8
20. Costela-Ruiz, V.J., Ilescas-Montes, R., Puerta-Puerta, J.M., Ruiz, C. and Melguizo-Rodríguez, L. (2020) SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 54, 62–75, https://doi.org/10.1016/j.cytogfr.2020.06.001
21. Natesh, R., Schwager, S., Sturrock, E. et al. (2003) Crystal structure of the human angiotensin-converting enzyme–lisinopril complex. Nature 421, 551–554, https://doi.org/10.1038/nature01370
22. Romero, J.C. and Reckelhoff, J.F. (1999) State-of-the-art lecture. Role of angiotensin and oxidative stress in essential hypertension. Hypertension 34, 943–949, https://doi.org/10.1161/01.HYP.34.4.934
23. Ajagopalan, S., Kurz, S., Münzel, T., Tarpey, M., Freeman, B.A., Griendling, K.K. et al. (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J. Clin. Invest. 97, 1916–1923, https://doi.org/10.1172/JCI116263
24. Varagic, J., Ahmad, S., Nigata, S. and Ferrario, C.M. (2014) ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Curr. Hypertens. Rep. 16, 420, https://doi.org/10.1007/s11906-014-0420-5
25. Brown, N.J. and Vaughan, D.E. (2000) Prothrombotic effects of angiotensin. Adv. Intern. Med. 45, 419–429
26. Rabelo, L., Altenina, N. and Bader, M. (2011) ACE2–angiotensin-(1–7)–Mas axis and oxidative stress in cardiovascular disease. Hypertens. Res. 34, 154–160, https://doi.org/10.1083/hr.2010.235
27 Yamaoka-Tojo, M. (2020) Endothelial glycocalyx damage as a systemic inflammatory microvascular endotheliopathy in COVID-19. *Biomed. J.* **43**, 399–413, https://doi.org/10.1016/bj.2020.08.007.

28 Iba, T. and Levy, J.H. (2019) Derangement of the endothelial glycocalyx in sepsis. *J. Thromb. Haemost.* **17**, 283–294, https://doi.org/10.1111/jth.14371.

29 Gúzik, T.J., Mussa, S., Gastaldi, D. et al. (2002) Mechanisms of increased vascular superoxide production in human diabetes mellitus: role of NAD(P)H oxidase and endothelial nitric oxide synthase. *Circulation* **105**, 1666–1662, https://doi.org/10.1161/01.CIR.0000012748.58444.08.

30 Jarajapu, Y.P.R., Bhattacharjee, S., Varma, S., Lenarcic, B., Aksoy, H., Yang, L. et al. (2013) Activation of the ACE2/Angiotensin-(1–7)/Mas Receptor Axis Enhances the Reparative Function of Dysfunctional Diabetic Endothelial Progenitors. *Diabetes* **62**, 1258–1269, https://doi.org/10.2337/db12-0808.

31 Shi, S., Qin, M., Shen, B. et al. (2020) Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol.* **5**, 802–810, https://doi.org/10.1001/jamacardio.2020.0950.

32 Patel, V.B. et al. (2016) Role of the ACE2/Angiotensin 1–7 axis of the renin–angiotensin system in heart failure. *Circ. Res.* **118**, 1313–1326, https://doi.org/10.1161/CIRCRESAHA.116.307708.

33 Renu, K., Prasanna, P.L. and Valsala Gopalakrishnan, A. (2020) Coronaviruses pathogenesis, comorbidities and multi-organ damage - a review. *Life Sci.* **255**, 117839, https://doi.org/10.1016/j.lfs.2020.117839.

34 McQuillan, L.P. et al. (1994) Hypoxia inhibits expression of eNOS via transcriptional and posttranscriptional mechanisms. *Am. J. Physiol.* **267**, H1921–H1927, https://doi.org/10.1152/ajpheart.1994.267.5.H1921.

35 Maniatis, N.A., Kotanidou, A., Catravas, J.D. and Orfanos, S.E. (2008) Endothelial pathomechanisms in acute lung injury. *Vasc. Pharmacol.* **49**, 119–133, https://doi.org/10.1016/j.vph.2008.06.009.

36 Burrell, L.M., Risvanis, J., Kubota, E., Dean, R.G., MacDonald, P.S., Lu, S. et al. (2005) Myocardial infarction increases ACE2 expression in rat and humans. *Eur. Heart J.* **26**, 369–375, https://doi.org/10.1093/eurheartj/ehu114.

37 Ruiz-Ortega, M., Ruperez, M., Esteban, V., Rodriguez-Vita, J., Sánchez-López, E., Carvajal, G. et al. (2006) Angiotensin II: a key factor in the inflammatory and fibrotic response in kidney diseases. *Nephrol. Dial. Transplant.* **21**, 16–20, https://doi.org/10.1093/ndt/gfl265.

38 Chalupsky, K. and Cai, H. (2005) Endothelial dihydrofolate reductase: critical for nitric oxide bioavailability and role in angiotensin II uncoupling of endothelial nitric oxide synthase. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 9056–9061, https://doi.org/10.1073/pnas.0409594102.

39 Bataineh, A. and Raij, L. (1998) Angiotensin II, nitric oxide, and end-organ damage in hypertension. *Kidney Int. Suppl.* **68**, S14–S19, https://doi.org/10.1046/j.1523-1755.1998.06806.x.

40 Imai, Y. et al. (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **436**, 112–116, https://doi.org/10.1038/nature03712.

41 Nowak, K., Weih, S., Metzger, R., Albrecht, II, R.F., Post, S., Hohenberger, P. et al. (2007) Immunotargeting of catalase to lung endothelium via anti-angiotensin-converting enzyme antibodies attenuates ischemia-reperfusion injury of the lung in vivo. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **293**, L162–L169, https://doi.org/10.1152/ajplung.00001.2007.

42 Bishop, T. and Ratcliffe, P.J. (2015) HIF hydroxylase pathways in cardiovascular physiology and medicine. *Circ. Res.* **117**, 65–79, https://doi.org/10.1161/CIRCRESAHA.117.305199.

43 Gu, H.F., Zheng, X., Seman, N.A., Gu, T., Botusan, I.R., Sunkari, V.G. et al. (2013) Impact of the hypoxia-inducible factor-1 α (HIF1α) Pro582Ser polymorphism on diabetes nephropathy. *Diabetes Care* **36**, 415–421, https://doi.org/10.2337/db12-1125.

44 Zhang, R. et al. (2009) Role of HIF-1α in the regulation ACE and ACE2 expression in hypoxic human pulmonary artery smooth muscle cells. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **297**, L631–L640, https://doi.org/10.1152/ajplung.90415.2008.

45 Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H. et al. (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir. Med.* **8**, 475–481, https://doi.org/10.1016/S2213-2600(20)30079-5.

46 Ras-Reyes, C., Zubieta-DeUríoste, N., Poma-Machicado, L. et al. (2020) Does the pathogenesis of SARS-CoV-2 virus decrease at high-altitude? *Respir. Physiol. Neurobiol.* **277**, 103443, https://doi.org/10.1016/j.resp.2020.103443.

47 Weidemann, A. and Johnson, R. (2008) Biology of HIF–1α. *Cell Death Differ.* **15**, 621–627, https://doi.org/10.1038/cdd.2008.12.

48 Kim, J.W., Tchernyshyov, I., Semenza, G.L. and Dang, C.V. (2006) HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* **3**, 177–185, https://doi.org/10.1016/j.cmet.2006.02.002.

49 Gupta, N. and Wish, J.B. (2017) Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am. J. Kidney Dis.* **69**, 815–826, https://doi.org/10.1053/j.ajkd.2016.12.011.

50 Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J.V., Pfeffer, M.A. and Solomon, S.D. (2020) Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. *N. Engl. J. Med.* **382**, 1653–1659, https://doi.org/10.1056/NEJMoa2005760.

51 Sommerstein, R. and Grani, C. (2020) Rapid response: preventing a Covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ* **368**, m810.

52 Statement from the American Heart Association, The Heart Failure Society of America and The American College of Cardiology (2020) Patients taking ACE-i and ARBs who contract COVID-19 should continue treatment, unless otherwise advised by their physician. https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-whocontract-covid-19-should-continue-treatment-unlessotherwise-advised-by-their-physician.

53 Kai, H. and Kai, M. (2020) Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. *Hypertens. Res.* **43**, 648–654, https://doi.org/10.1080/s41440-020-0455-8.