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VIEWPOINT

The dilemma of renin–angiotensin system inhibitors in coronavirus disease 2019 (COVID-19): insights into lung fluid handling and gas exchange in heart failure patients

Marco Guazzi* and Alice Moroni

Cardiology University Department, IRCCS Policlinico San Donato, University of Milan, Milan, Italy

The coronavirus disease 2019 (COVID-19) pandemic is precipitating the global health crisis of our time, as stated by the World Health Organization (WHO). Since its surge in December 2019, in Wuhan, Hubei province, China, the virus has spread to every continent except Antarctica. The main clinical manifestation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is severe respiratory infection, which yields to inflammatory reaction and alveolar fluid floading, ultimately impairing gas exchange.[1–3]

Reports have clearly established that hypertension, diabetes, and cardiovascular diseases are the most frequent comorbidities in affected patients, and these individuals are exposed to the highest mortality rates.[4,5]

Most of these patients suffer from pre-existing or rapidly evolving heart failure (HF)[6,7] and are commonly treated with renin–angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), according to guideline class I, level of evidence A.[8] However, there is an ongoing debate about the use of ACEIs/ARBs in patients with COVID-19 or at risk of SARS-CoV-2 infection which may not be beneficial or even harmful.[9] Vaduganathan *et al.*[10] have recently reported an elegant and comprehensive review on the controversial aspects of this topic, providing the most updated evidence.

We gained previous experience on the effects of renin–angiotensin system inhibition on the pulmonary function of HF patients showing a protective effect on the perturbed gas exchange and lung fluid handling, i.e. alveolar–capillary stress failure, an effect especially observed with enalapril treatment, with a positive but not statistically significant trend for losartan[11,12].

Based on this, we outline how renin–angiotensin inhibitors may interact with lung fluid handling and gas diffusion process in patients with HF infected by SARS-CoV-2, and propose areas for further research.

Both ACE and ACE2 are homologous enzymes part of the ACE family of the dipeptidyl and monopeptidyl carboxydipeptidases, respectively, with different key functions in the renin–angiotensin system. ACE cleaves angiotensin (Ang) I to angiotensin (Ang) II, which in turn binds and activates Ang II receptors type 1 and type 2. Activation of type 1 receptors leads to vasoconstrictive, pro-inflammatory, and pro-oxidative effects. ACE2 mediates the conversion of Ang II to Ang-(1–7), which binds to the Mas receptor and promotes anti-inflammatory, antioxidative, and vasodilatory effects.[13]

All these effects are well studied and documented for the systemic circulation, but information regarding their activity in the pulmonary microcirculation is mostly lacking.

Interestingly, ACE is produced in the lung tissue and released by the pulmonary circulation. In humans, ACE2 is predominantly expressed in the alveolar type II cells and enterocytes of the small intestine.[14]

SARS-CoV-2 utilizes lung ACE2 as an essential receptor for cell entry and host cellular proteases into the alveolar type II cells. Namely, the spike (S) protein of SARS-CoV-2 is primed by a transmembrane cellular serine protease, TMPRSS2, which allows fusion of viral and cellular membranes.[15]

Physiologically, fluid handling across the alveolar gas barrier is modulated by cellular and molecular mechanisms of ions and fluid transposition as depicted in *Figure 1*. The alveolar surface is continuously cleared by the excess of fluid through the activity of energy-independent epithelial sodium channels and aquaporins.[16] Fluid is then transposed by ATP Na^+/K^+ pumps into the vascular compartment. These protective pathways, which are essential to keep the alveolar surface dry and guarantee gas exchange, are highly challenged by a number of haemodynamic, inflammatory and growth factor stimuli typical of the HF syndrome.[3,17] Interstitial fibrosis and capillary remodelling ensue when the fluid triggers the

*Corresponding author. Heart Failure Unit-Cardiology, Department of Biomedical Sciences for Health, IRCCS Policlinico San Donato, University of Milan, Piazza E. Malan 2, 20097 San Donato Milanese, Milan, Italy. Tel/Fax: +39 02 52774966, Email: marco.guazzi@unimi.it

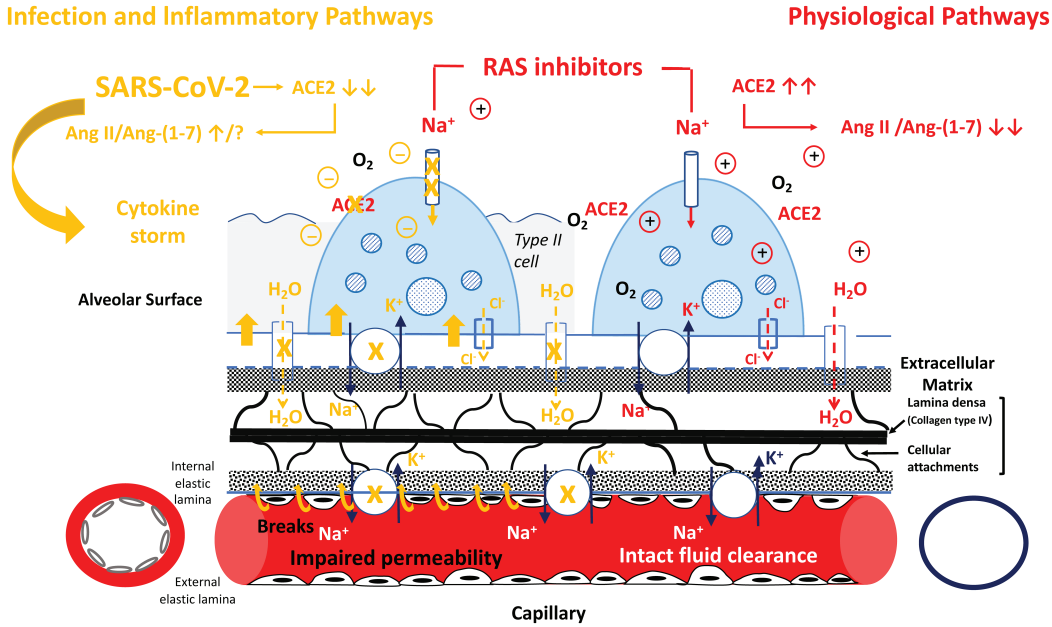

Figure 1 Schematic representation of fluid handling through the alveolar–capillary barrier and potential effects of renin–angiotensin system (RAS) inhibition and angiotensin-converting enzyme 2 (ACE2) levels in the normal and COVID-19 condition. Fluid is continuously removed from the alveoli (type II pneumocytes) to the interstitium by epithelial Na^+ channels and aquaporins. Then removal of fluid from the interstitium to the vascular compartment is driven by osmosis and Na^+/K^+ ATPase pump. These mechanisms are essential for guaranteeing an efficient gas exchange. Multiple conditions, and primarily heart failure, challenge the integrity of the alveolar–capillary unit and the functional response of these molecular mechanisms. The best *in vivo* method to assess how these systems work is measuring gas exchange. Studies performed in heart failure patients under treatment with RAS blockade, especially angiotensin-converting enzyme inhibitors, investigating the gas exchange response under fluid loading have shown a facilitating effect on alveolar–capillary membrane gas diffusion. This effect would be mediated by high ACE2-induced angiotensin (Ang)-(1–7) production and low Ang II. SARS-CoV-2 binds to ACE2 for entering and injuring type II cells, leading to an inflammatory reaction and cytokine release. ACE2 expression is down-regulated in experimental models of acute respiratory distress syndrome, and overexpression of ACE2 in null models is beneficial. RAS inhibitors (angiotensin-converting enzyme inhibitors and primarily angiotensin receptor blockers) stimulate ACE2 synthesis and Ang II conversion to Ang-(1–7), which may be of benefit or even harmful according to the degree of affinity and the reciprocal neutralizing effects between ACE2 and SARS-CoV-2.

inflammatory cascade and connective tissue reaction.[18] In HF with pulmonary congestion and inflammation and even some reactive interstitial fibrosis, renin–angiotensin system blockade by ACEI has been shown to promote a protective effect on lung fluid swelling from capillaries to interstitium and 'speed up' fluid clearance during saline loading with improved gas exchange.[11,12,19]

The infection by SARS-CoV-2 specifically challenges and disrupts the fine protective mechanisms of ion regulatory transport and precipitates the edematous inflammatory cascade.[20]

Renin–angiotensin system blockade increases ACE2 over-expression and in SARS-CoV-2 free conditions there is a strong rationale that ACE2 may mediate these beneficial effects.[21,22]

Thus, in conditions of SARS-CoV-2 infection, the ACE2 activity appears down-regulated yielding an unfavourable Ang II/Ang-(1–7) balance.[23] Of note, Ang-(1–7) plays a crucial protective role against lung inflammation. Specifically, this heptapeptide inhibits alveolar apoptosis, limits the synthesis of cytokines, and attenuates endothelial cell activation and the loss of barrier function and oedema.[24]

Experimental models of genetically-modified mice undergoing acute lung injury have documented an ACE2 protein down-regulation by binding its spike protein, and this loss leads to a leaky capillary effect through stimulation of Ang II receptor type 1.[25] Interestingly enough, the ACE2 knockout strain exhibited the worse edematous and inflammatory response and pre-treatment with exogenous recombinant human ACE2 attenuated acute lung failure in ACE2 knockout as well as in wild-type mice.[25]

Additional experimental observations looking at hyperoxia treatment showed significant reduction in lung ACE2 expression/activity and increased Ang II/Ang-(1–7) ratio in adult mice exposed to 95% oxygen for 72 h. It has also been demonstrated that activation of ACE2 can reduce the severity of hyperoxic lung injury by inhibiting inflammatory response and oxidative stress, and that ACE2 can inhibit the NF-kB and activate the Nrf2/HO-1/NQO1 pathways, which may be involved in the underlying mechanism.[26] A pre-COVID-19 trial of ACE2 infusion in 10 patients with acute respiratory distress syndrome was completed in humans but was not powered to show efficacy on gas exchange.[27]

A main question, however, is whether SARS-CoV-2 ability to neutralize ACE2 activity is powerful enough to neutralize the additive protection of ACE2 over-expression, definitively leading to an untoward negative cascade of lung fluid compartmentalization, ventilation/perfusion mismatch and impaired gas exchange.

This key issue will likely be clarified soon but, meanwhile, reasoning on this double edge front, it is tempting to speculate that ARBs could divert a larger amount of Ang II to ACE2 activity, even though it remains unpredictable what level of benefit or harm could be observed with ARBs vs. ACEIs.

In this rapidly evolving pandemic scenario, the present observations could enhance our understanding on how treatment with renin–angiotensin system inhibitors may impact COVID-19 HF patients. Accordingly, we highly advocate that upcoming basic science and clinical proof of concept studies should scrutinize the aforementioned working hypotheses and theories. On one hand, pre-clinical studies should be planned for definitively establishing the interaction between molecular pathways involved in alveolar–capillary fluid handling and ACE2 activity in knockout ACE2 −/− vs. ACE2 +/+ animal models of SAR-CoV-2 lung injury. On the other hand, clinical studies should recruit SARS-CoV-2 asymptomatic carriers to test how renin–angiotensin system inhibition, by randomization to ACEI or ARB, could impact on fluid homeostasis and gas exchange processes by mitigating or worsening their fundamental physiology, peculiarly threatened by SARS-CoV-2 infection.

Conflict of interest: none declared.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;**382**:1708–1720.
2. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, Van der Werf S, Yazdanpanah Y. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *Lancet Infect Dis* 2020;**20**:697–706.
3. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail* 2008;**14**:695–702.
4. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, Chao Y, Yang Z, Xu J, Zhou X, Chen D, Xiong W, Xu L, Zhou F, Jiang J, Bai C, Zheng J, Song Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;**180**:1–11.
5. Wang L, He W, Yu X, Hu D, Bao M, Liu H, Zhou J, Jiang H. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;**80**:639–645.
6. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020 Mar 27. https://doi.org/10.1001/jamacardio.2020.1096 [Epub ahead of print].
7. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res* 2020;**116**:1097–1100.
8. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
9. Sommerstein R, Gräni C. Re: preventing a covid-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19. *BMJ* 2020;**368**:m810.
10. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020;**382**:1653–1659.
11. Guazzi M, Marenzi G, Alimento M, Contini M, Agostoni P. Improvement of alveolar-capillary membrane diffusing capacity with enalapril in chronic heart failure and counteracting effect of aspirin. *Circulation* 1997;**95**:1930–1936.
12. Guazzi M, Agostoni P, Guazzi MD. Modulation of alveolar-capillary sodium handling as a mechanism of protection of gas transfer by enalapril, and not by losartan, in chronic heart failure. *J Am Coll Cardiol* 2001;**37**:398–406.
13. Santos RA, Oudit GY, Verano-Braga T, Canta G, Steckelings UM, Bader M. The renin-angiotensin system: going beyond the classical paradigms. *Am J Physiol Heart Circ Physiol* 2019;**316**:H958–H970.
14. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004;**203**:631–637.
15. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**:271–280.e8.
16. Matthay MA, Folkesson HG, Verkman AS. Salt and water transport across alveolar and distal airway epithelia in the adult lung. *Am J Physiol* 1996;**270**:L487–L503.
17. Verbrugge FH, Guazzi M, Testani J, Borlaug B. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and the kidney. *Circulation* 2020, in press.
18. Guazzi M, Phillips SA, Arena R, Lavie CJ. Endothelial dysfunction and lung capillary injury in cardiovascular diseases. *Prog Cardiovasc Dis* 2015;**57**:454–462.
19. Guazzi M, Brambilla R, Agostoni P, Guazzi MD. Influence of ACE-inhibition on salt-mediated worsening of pulmonary gas exchange in heart failure. *Br J Clin Pharmacol* 2001;**51**:482–487.
20. Peteranderl C, Sznajder JI, Herold S, Lecuona E. Inflammatory responses regulating alveolar ion transport during pulmonary infections. *Front Immunol* 2017;**8**:446.
21. Deng J, Wang DX, Deng W, Li CY, Tong J. The effect of endogenous angiotensin II on alveolar fluid clearance in rats with acute lung injury. *Can Respir J* 2012;**19**:311–318.
22. Shenoy V, Ferreira AJ, Qi Y, Fraga-Silva RA, Diez-Freire C, Dooies A, Jun JY, Sriramula S, Mariappan N, Pourang D, Venugopal CS, Francis J, Reudelhuber T, Santos RA, Patel JM, Raizada MK, Katovich MJ. The angiotensin-converting enzyme 2/angiogenesis-(1-7)/Mas axis confers cardiopulmonary protection against lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2010;**182**:1065–1072.
23. Peiro C, Moncada S. Substituting angiotensin-(1-7) to prevent lung damage in SARSCoV2 infection? *Circulation* 2020;**141**:1665–1666.
24. Santos RA, Sampaio WO, Alzamora AC, Motta-Santos D, Alenina N, Bader M, Campagnole-Santos MJ. The ACE2/angiotensin-(1-7)/MAS axis of the renin-angiotensin system: focus on angiotensin-(1-7). *Physiol Rev* 2018;**98**:505–553.
25. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;**436**:112–116.
26. Fang Y, Gao F, Liu Z. Angiotensin-converting enzyme 2 attenuates inflammatory response and oxidative stress in hyperoxic lung injury by regulating NF-kappaB and Nrf2 pathways. *QJM* 2019;**112**:914–924.
27. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, Hall R, Poirier G, Ronco JJ, Tidswell M, Hardes K, Powley WM, Wright TJ, Siederer SK, Fairman DA, Lipson DA, Bayliffe AI, Lazaar AL. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. *Crit Care* 2017;**21**:234.