

COVID-19: strange new virus, endothelium and lessons learned from a pandemic

Uncertainty breeds fears

ENRIQUE MELGAREJO-ROJAS • BOGOTÁ, D.C. (COLOMBIA)

DOI: <https://doi.org/10.36104/amc.2020.1918>

The COVID-19 pandemic surprised humanity through an unknown virus and its “strange” behavior, for which we were obviously not prepared and which, due to its characteristics, became an epidemic after two months and only one month later a pandemic, and may ultimately mutate to an endemic. To date (August 13), it has caused 758,761 deaths with an average mortality rate of 3.6% and a total of 21,079,074 confirmed cases. In Colombia, 433,805 confirmed cases and 14,451 deaths have been reported, to date, with a mortality of 3.26%.

It began, apparently, on December 31, 2019, when a cluster of cases of pneumonia of unknown etiology was reported in Wuhan, Hubei Province, China. On January 9, 2020, the Chinese Center for the Control and Prevention of Diseases reported that the etiological agent was a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by SARS-CoV-2 was subsequently named COVID-19 by WHO (2, 3).

As is known, this virus uses angiotensin-converting enzyme 2 (ACE2) from the renin-angiotensin system as the entry receptor, initially in type II pulmonary alveolar epithelial cells (including cilia) (4, 5).

It may manifest as a simple “cold” or flu without major consequences, but some cases may present deregulation of the immune system associated with endothelial alteration - endotheliitis, really, and even a viral sepsis - with an exaggerated inflammatory, immunological and prothrombotic response and systemic manifestations, which may ultimately lead to multi-organ failure and death. This has been called a “cytokine storm” due to the overexpression of these polymorphic and complex molecules, triggering an unusual systemic increase of (IL)-2, IL-6, IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10e (CXCL10), chemokine (C-C motif) ligand 2 (CCL2), tumor necrosis factor alpha (TNF α), and interferon C, in addition to ferritin, with the latter leading to early worsening of tissue and cellular oxygenation (6-8).

Some of these cytokines are also involved in hypertensive disease; thus, uncontrolled arterial hypertension (HTN) or HTN which is not treated as a comorbidity is a marker for greater mortality in COVID-19 patients (9). Lymphopenia is a common and early finding, and a degree of correlation has recently been found between the severity or chronicity of HTN and lymphocytes (9-11), with a greater elevation of proinflammatory cytokines in uncontrolled hypertensive patients, especially if they are lymphopenic. That is, there is a coincidence correlation between the COVID-19 inflammatory response and hypertension (which ultimately has a vascular inflammatory effect, including arterial stiffness and biomechanical alterations) (12, 13).

This said, it is not surprising that type 2 diabetes mellitus (T2DM) has also proven to be a high impact comorbidity, considering that it is a disease associated with an inflammatory-oxidative state with early and accelerated endothelial dysfunction. The same occurs with heart failure (vascular inflammation, arterial stiffness and oxidation) and obesity, in which the adipocyte is an AgII augments with its consequent propensity towards, and facilitation of, inflammation and oxidation (14-16).

Initially, there was controversy due to confusion regarding the blocking of the renin-angiotensin system by ACE inhibitors or ARBs possibly magnifying the damage from or risk for COVID-19 through overexpression of the ACE-2 receptor by these medications.

Dr. Enrique Melgarejo-Rojas: FACC, FESC.
 Profesor Emérito Hospital Militar Central.
 Coordinador Grupo de Trabajo Medicina Vas-
 cular, Sociedad Colombiana de Cardiología.
 Bogotá, D.C. (Colombia).
 Correspondencia: Dr. Enrique Melgarejo-Rojas.
 Bogotá, D.C. (Colombia).
 E.mail: enrique.melgarejo@gmail.com
 Received: 16/VI/2020 Accepted: 23/VII/2020

However, this enzyme is structurally and biologically different from circulating and tissue ACE. Angiotensin converting enzyme-2 is an AgII counter-regulator, converting it to Ag 1-7, which, through its action on the Mas receptors, causes a completely antagonistic response to the “bad” angiotensin II, including neutralization of its inflammatory effect. It also stimulates the production of nitric oxide (NO) with all its recognized vascular benefits (anti-inflammatory, antiproliferative, antifibrotic, antioxidant, antithrombotic, profibrinolytic, antiatherogenic, etc.). As SARS-CoV-2 is internalized in the cell after binding to the receptor, it cleaves ACE-2, with the help of ADAM17 (17) (which is a disintegrin and metalloprotease transmembrane protein (18) activated by the viral S protein), leading to its elimination from the cell surface on cell penetration, thus allowing AgII to do all its damage without anything to counterregulate it; this is where the real damage begins. However, ADAM-17 converts the ACE-2 to circulating ACE-2, which is not influenced by ACE inhibitors or ARBs.

Worsening the situation, the reduction of pulmonary ACE-2 activates bradykinin receptor B1 (BKR1), causing greater inflammation and vascular damage, not just in the lungs but also in other organs (through stimulatory G protein). This shows the interrelationship between the kallikrein-kinin system (KKS) and the renin-angiotensin system (RAS) (17).

Furthermore, epidemiological studies have shown that hypertensive patients who take renin-angiotensin system inhibitors (RASi) (ACE inhibitors, ARBs) have a lower incidence of community-acquired pneumonia, which dispels the myth of risk in using these inhibitors in COVID-19 (18).

There have also been recent publications in which no increase in mortality has been seen with the use of RASi in infected patients, clearing up the unfounded fear that inhibitors of this system, in overexpressing the ACE-2 receptors, would facilitate SARS-CoV-2 injury or lethality, which is far from plausibility and reality. In this regard, the data show that, in a series of 1,128 hypertensive patients with COVID-19 in a retrospective, multi-center study, there was lower mortality in patients receiving RASi (3.7% vs. 9.8%; $P = 0.01$) (19).

Another analysis of a registry of 8,910 patients did not show increased mortality with the use of RASi, either (20). In addition, the RA system is linked to the natriuretic peptide system, another counterregulatory system which stimulates diuresis, natriuresis and vasodilation. Natriuretic peptides are inactivated by neprilysin (neutral endopeptidase, NEP), whose inhibition by sacubitril activates the MasR pathway through production of Ang 1-7 from AngII (an action similar to that of ACE-2). This is what we know today as angiotensin receptor neprilysin inhibitors (ARNi). As is widely known, sacubitril together with an angiotensin II receptor blocker has marked a turning point in the management of heart failure, which is even now recognized by the various (2017) ACC/AHA/ACCF guidelines for heart failure management (21).

It has already been mentioned that ACE2 is expressed in the lung (alveolar epithelial cells) and other tissues including

the brain, kidney, gastrointestinal tract, adipose tissue, testicles, cardiomyocytes, and, to varying degrees, in the blood vessels (vascular endothelial and smooth muscle cells). That is, it involves the vessel wall and its temple: the endothelium. This endothelial damage caused by SARS-CoV-2 and its inflammatory response may destabilize vulnerable atherosclerotic plaques, as well as induce inflammation and/or cardiac cytotoxicity and activate the coagulation cascade, leading to a hypercoagulable state and, ultimately, to disseminated intravascular coagulation (22, 23). Autopsy studies (which were initially sparse) documented that COVID-19 was not a “simple viral pneumonia”. As was mentioned previously, there was micro and macrothrombotic involvement arising from endothelial and vascular damage, with an initial microthrombotic component, which explains the hypoxemia in as yet asymptomatic patients. This led to subsequent angiogenesis disorders and expression of cardiac injury biomarkers as manifestations of depressed ventricular function and arrhythmias (worsened by chloroquine, hydroxychloroquine, azithromycin and other medications which prolong the electrocardiographic QT interval), coupled with hydroelectrolytic imbalance (especially hypokalemia and/or hypomagnesemia). There are manifestations of direct cardiotoxicity (24-26), including elevated troponins. This cardiotoxicity has been shown through magnetic resonance and echocardiography, documenting cardiomyopathy due to acute cardiac stress (takotsubo) (27).

Furthermore, prolonged immobility, coupled with endothelial dysfunction, inflammation and a prothrombotic state also facilitates deep vein thrombosis and/or pulmonary embolism, shown clinically by increased D-dimer and fibrinogen. Elevation of these two markers already indicates a poor prognosis (28).

Faced with the evidence that young people without apparent comorbidities have also died, endothelial dysfunction in the subclinical stage may be the explanation. Non-invasive assessment of endothelial function or detection of dysfunction (in addition to biomarkers and imaging) in young, infected individuals could be a way to predict the risk of complications in this population group. This is a topic that will need to be considered; time will tell.

In summary, the COVID-19 pandemic, at a vascular system level in the vulnerable population, causes early, progressive and severe endothelial dysfunction, although, fortunately, in a low percentage (according to various reports, from 3-7%). It causes concomitant early hypoxemia, cytokine storm, cardiotoxicity and disseminated intravascular coagulation, manifesting clinically in heart failure, infarctions in general, arrhythmias and venous thromboembolism, multiple system failure and death.

Specifically, at the cardiac level, various series have reported heart failure, malignant ventricular arrhythmias (torsades de pointes, ventricular tachycardia and ventricular fibrillation), cardiogenic shock, myocarditis and acute *cor pulmonale* or PTE. So many cardiovascular-systemic com-

plications were not to be expected with a coronavirus, and, therefore, we have not yet learned to manage it, since there are various stages of severity, ranging from mild symptoms to cardiovascular and systemic collapse.

Conclusions and lessons learned

A new, atypical virus has arrived, among other reasons, because of its high capacity for spreading and dissemination, even, atypically, its dissemination in the asymptomatic stage. Although its lethality is not very high compared to SARS-2 and MERS (also caused by a coronavirus), Ebola and other epidemics such as dengue, chikungunya, etc., it has caused greater mortality than SARS and MERS (29). This high mortality is due to its rapid diffusion, and, as has been mentioned, its transmission in the asymptomatic stage, as well as the lack of specific treatment, a lack of knowledge, and a lack of strong education of the community which, due to ignorance, does not have a culture of self-confinement and, even worse, of self-care. However, the impact on healthcare systems - including the saturation of ICU capacity - together with the worldwide and geopolitical socioeconomic impact, coupled with the continued lack of a specific treatment and the logical delay in vaccine availability (because, to complicate matters further, it is a mutating virus, which will make the classification of its most pathogenic strain(s) more difficult), all seem to indicate that SARS-CoV-2 has arrived to stay endemically, just like influenza and HIV. That is, we will go from a pandemic to an endemic. And contrary to what was originally thought, (that the treatment was the same as for SARS-type pneumonia), ventilators have not been the answer. Subjecting an inflamed and microthrombotic lung to pressure and volume loads has proven to not be the magical nor rational solution, as the statistics show (30, 31).

And perhaps the most serious problem we face is fear, which paralyzes our behavior and may even be more serious than the pandemic, as well as the post-COVID syndrome or the coronavirus tsunami. That is, its sequelae and possible aftershocks (such as residual pulmonary fibrosis in people who have recovered, post-pulmonary embolism syndrome, post-prolonged ICU syndrome added to post-traumatic stress, associated with anxiety-depression, residual or worsened heart failure, fractures, prolonged convalescence, etc.). All of this coupled with global socioeconomic and geopolitical problems due to increased poverty, soaring unemployment, malnutrition, severe sarcopenia in elderly persons who have been indiscriminately and excessively confined, osteoporosis, deaths at home due to complications of non-COVID diseases, and a perhaps never before seen phenomenon: a flood of heart failures, uncontrolled diabetes, uncontrolled HTN, unattended coronary disease, and more advanced arrhythmias, among others, which will present to the hospitals en masse, because the patients held back from seeking prompt care for “fear that I will catch the virus in the hospital.” In addition, the postponement of interventionism and “non-emergent” surgeries will explode

and also significantly overrun the healthcare system. We are facing a rapidly disseminating pandemic (globalization, airports and airplanes which transport COVID at more than 900 km/hr), coupled with not being prepared with human resources, technology, or massive testing. Testing, not just as a “daily statistic”, but rather to take epidemiological hedging measures, not shutting up healthy and sick people due to political decisions. In addition, the evident shortfalls in the national healthcare systems, especially their regional fragility due to the abandonment of the concept of health caused by the chronic counterproductive work of politicians, and sorely aggravated by the other national epidemic-endemic: corruption, which is perhaps more serious and has been chronically more lethal than COVID-19 itself. This is an inhuman attitude which is difficult to understand.

All that remains is for us to act on what is evident for now: the most effective and least costly, but very emotionally difficult, measures such as social distancing to avoid a high viral load for the ACE2 receptor, as has been shown in a meta-analysis recently published in *Lancet* (32). The proper use of face masks, avoiding touching the face and eyes, and maintaining a distance of more than one meter between people are ultimately the most effective measures. Displays of affection with handshakes, hugs and kisses have had to be postponed for nobody knows how long. But as long as we have words to express our affection, this is the rational change. And a crucial point is to educate and raise awareness in people that this is not just another “bad cold”. No, this is an unknown disease which arrived no one knows how, and arrived to stay for an unknown length of time and with new outbreaks in already infected patients. Many of our habits have changed, but with the hope that maybe we ourselves will change or that we will discover ourselves in the solitude of confinement and will reconsider our attitude of solidarity towards others and towards mother nature, caring for our home: planet Earth, which may in some way be manifesting itself against the depredation of the Anthropocene. This may be the only or last opportunity, which may not return.

An ultramicroscopic structure has effectively changed our “normality”. In theory, it would be encouraging for The Little Prince to return from the B612 asteroid to kindly tell us about the strange way in which we adults view life. However, our irrationality and the human condition of which Anna Arendt spoke so much, allows us to glimpse a no returning to “normal”. We will doubtless go back to living in a different way, coexisting with one more virus while science (now more highly valued) manages to contain it and we earthlings will hopefully have learned something from the behavior of other species: to unite in the face of threats; in our case, in the face of uncertainty.

References

1. WHO. Disponible: App Covid 19 WHO, Worldometers, info, JHU -Apple-store, Android
2. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C-L, Chen H-D, Chen J, Luo Y, Guo H, Jiang R-D, Liu M-Q, Chen

- Y, Shen X-R, Wang X, Zheng X-S, Zhao K, Chen Q-J, Deng F, Liu L-L, Yan B, Zhan F-X, Wang Y-Y, Xiao, G-F, Shi Z-L.** A pneumonia outbreak associated with a new coronavirus of probable, bat origin. *Nature* 2020;579:270–273.
3. <http://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic>. (30 March 2020)
 4. **Hoffman M, Klein-weber, Schroeder s et al.** SARS-Cov-2 Cell entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease.(2020) *Cell* 181,52; 271/280.
 5. **Hirano T, Murakami M.** 2020. *Immunity* 52, 731/733.COVID-19: a New Virus, but a Familiar Receptor and Cytokine Release Syndrome.
 6. **Wong CK, Lam CWK, Wu AKL, et al.** Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 2004;136 (1):95–103 2020. ACE Inhibitors and ARBs: Good, Bad, or Neutral in COVID-19 Patients?
 7. **Ruan Q, Yang K, Wang W, et al.** Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. 2020 *Intensive Care Med* 46, 846, 848.
 8. **Klok FA, Kruip MJHA, van der Meer NJM, et al.** Incidence of thrombotic complications in critically ill ICU patients with COVID-19. 2020. *Thromb Res* .191:145-147.
 9. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. 2020 Mar 28;395(10229):1038] [published correction appears in *Lancet*. 2020 Mar
 10. **Siedlinski M, Jozefczuk E, Xu X, Teumer A, Evangelou E, Schnabel RB, Welsh P, Maffia P, Erdmann J, Tomaszewski M, Caulfield MJ, Sattar N, Holmes MV, Guzik TJ.** White blood cells and blood pressure: a Mendelian randomization study. 2020. *Circulation* .119.045102.
 11. **M, Mikolajczyk T, Sliwa T, Dikalov S, Weyand CM, Guzik TJ, Harrison DG.** Hypertension and increased endothelial mechanical stretch promote monocyte differentiation and activation: roles of STAT3, interleukin 6 and hydrogen peroxide. *Cardiovasc Res* 2018; **114**: 1547–1563.
 12. **Gavin Y Oudit ; Marc A Pfeffer.** Plasma angiotensin-converting enzyme 2: novel biomarker in heart failure with implications for COVID-European Heart J. Volume 41 Issue 19. 14 May 2020. <https://doi.org/10.1093/eurheartj/ehaa414>.
 13. **Mitchell GF, Guo CY, Benjamin EJ, et al.** - Cross-sectional correlates of increased aortic stiffness in the community: the Framingham Heart Study. *Circulation*. 2007; **115**: 2628–2636.
 14. **Avogrp A, Albiero M, Mangazzo L et al.** *Diabetes Care* 2011, Diabetes Mellitus-2 }; an inflammatory state. 34 Suppl 2 .S285-290.
 15. **Drexler H.** Endothelium as Thrapeutic Target in Hert Failure. *Circulation* (1999) 98, 2252-5.
 16. **Ellulu MS, Patimah I, Khaza' ai H, Rahmat A, Abed Y.** Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13(4):851-863. doi:10.5114/aoms.2016.58928
 17. **Kreutz R, Algharably EAE, Azizi M, et al.** Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. *Cardiovasc Res*. 2020;116(10):1688-1699. doi:10.1093/cvr/cvaa097
 18. **Janssen DJA, Ekström M, Currow DC, et al.** COVID-19: Guidance on Palliative care from a European Respiratory Society International Task Force [published online ahead of print, 2020 Jul 16]. *Eur Respir J*. 2020;2002583. doi:10.1183/13993003.02583-2020
 19. **Wu A, Good C, Downs JR, Fine MJ, Pugh MJ, Anzueto A, Mortensen EM.** The association of cardioprotective medications with pneumonia-related outcomes. *PLoS One* 2014;9:e85797
 20. **Rohit L, Liu PP and Li H.** Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19. *Circ Res*. 2020, 10.1161/CIRCRESAHA.120.317134
 21. **Yancy CW, Jessup M, Bozkurt B, et al.** 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation*. 2017;136(6):e137-e161. doi:10.1161/CIR.0000000000000509
 22. **Liang Chen1, Xiangjie Li ,Mingquan Chen, Yi Feng Chenglong Xiong.** The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-19. *Cardiovascular Research* (2020) 116, 1097–1100.
 23. **Levi M, van der Poll T, Büller HR.** Bidirectional relation between inflammation and coagulation. *Circulation* 2004;109:2698–704.
 24. **Prabhu SD.** Cytokine-induced modulation of cardiac function. *Circ Res*. 2004;95 (12):1140–53.
 25. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–62.
 26. **Zheng YY, Ma YT, Zhang JY, Xie X.** COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259-260. doi:10.1038/s41569-020-0360-5
 27. **Sala S, Peretto G, Gramegna M, et al.** Acute myocarditis presenting as a reverse TakoTsubo syndrome in a patient with SARS-CoV-2 respiratory infection. 2020 *Eur Heart J* 2020. doi:10.1093/eurheartj/ehaa286.
 28. **Meizlish M, Pine A, Goshua G, et al.** Circulating Markers of Angiogenesis and Endotheliopathy in COVID-19. Preprint. *medRxiv*. 2020;2020.06.29.20140376. Published 2020 Jul 1. doi:10.1101/2020.06.29.20140376
 29. **Mahase E.** Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ*. 2020;368:m641. Published 2020 Feb 18. doi:10.1136/bmj.m641
 30. **Marini JJ, Rocco PRM, Gattinoni L.** Static and Dynamic Contributors to Ventilator-induced Lung Injury in Clinical Practice. Pressure, Energy, and Power. *Am J Respir Crit Care Med*. 2020;201(7):767-774. doi:10.1164/rccm.201908-1545CI
 31. **Patel BK, Kress JP, Hall JB.** Alternatives to Invasive Ventilation in the COVID-19 Pandemic [published online ahead of print, 2020 Jun 4]. *JAMA*. 2020;10.1001/jama.2020.9611. doi:10.1001/jama.2020.9611
 32. https://www.acc.org/latest-in-cardiology/journal-scans/2020/06/08/12/37/physical-distancing-face-masks-and-eye-protection?utm_source=accupdate&utm_medium=email_newsletter&utm_content=20200612&utm_campaign=accupdate.

