EDITORIAL

Cardiovascular complications of COVID-19: evidence, misconceptions, and new opportunities

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On June 01, 2020, the outbreak of COVID-19 caused by SARS-CoV-2 has escalated to 6.3 million cases worldwide, including 374,000 deaths. Severe lung disease with acute respiratory distress syndrome represents one of the most common complications. Additionally, myocardial injury is present in more than a quarter of critical cases, manifesting either acutely on presentation or more insidiously as illness severity intensifies (1, 2, 3, 4).

Clinical signs of cardiovascular disease include chest pain, fulminant myocarditis, arrhythmias, acute coronary artery disease, and heart failure. More recently, microvascular disease syndromes have been reported, including cutaneous reticular livedo (5, 6). Some cases of Kawasaki disease, in which blood vessels throughout the body become inflamed and can form aneurysms, have been also reported. However, this figure is lower than would be normally expected at this time of year when Kawasaki disease generally peaks (<https://www.rcpch.ac.uk/news-events/news/college-responds-recent-reports-covid-19-children>).

Media articles on Kawasaki disease were confusing and have caused public concern. This calls for cautious interpretation and communication of research outputs, a difficult task in a global emergency requiring immediate medical solutions. Two COVID-19 priority studies in the UK (DIAMONDS (Central Portfolio Management System 45537) and ISARIC (UK Clinical Research Network 14152)) are collaborating in a study exploring prevalence of the disease and underpinning mechanisms.

Researchers around the world are racing to learn how the virus behaves and which health factors put people most at risk. The crucial question they are trying to work out is whether there may be some specific mechanism in

cells of the lung and heart that could mean some people suffer respiratory complications and heart attacks more than others. While the increased frailty of cardiovascular patients may account for the susceptibility to infection and organ damage, the reason why COVID-19 causes cardiovascular complications is less obvious.

SARS-CoV-2 has adopted a successful tactic to infect, damage, and spread. The virus binds with its spike protein to the surface receptor angiotensin converting enzyme 2 (ACE2) to unlock human cells and begin infection. We know relatively little of the stoichiometry of the virus – human cell receptor interaction. The minimum number necessary for infection varies between different viruses and it is not clear what is minimum infectious dose for COVID-19. Likewise, it remains to be established whether repeated exposures or a single contact with massive doses of the virus, like in the case of clinical staff caring patients who are not known to be infected, can increase the risk of developing severe forms of the disease.

The second element to consider is the binding affinity of the viral spike protein for the human cell receptor. The binding of SARS-CoV-2 to ACE2 is stronger than previous coronaviruses, due to difference in key amino acid residues allowing for enhanced interactions between the virus and human cells. This may explain the larger global impact of COVID-19 as compared with SARS. Interfering with binding of SARS-CoV-2 to ACE2 could be a means to attenuate infection, while waiting for vaccine availability. In this respect, the use of the extracellular domain of ACE2 could represent a solution to sponge the virus before it can reach cell membrane bound ACE2 receptors. It is not clear whether having high circulating levels of ACE2 are protective, neutral, or negative in terms

of risk of infection and disease severity and if there is a relationship, either positive or negative, between the levels of soluble and membrane bound ACE2. A recent study has shown a modest increase of circulating ACE2 in men with cardiovascular disease, with no significant difference between those on ACE inhibitors vs other treatments (7). The authors have extrapolated this into an increase risk for COVID-19 in men, but no data have been reported in COVID-19 patients and the observed difference was small in magnitude and of uncertain relevance for explaining a higher prevalence of COVID-19 between sexes.

The third and most debated stoichiometric variable is represented by the number of receptors expressed on the surface of cells. As yet, the possibility that severity and type of complications are influenced by ACE2 expression levels in different organs is contradictory and unsupported by causative evidence. We just do not know if having high or low ACE2 expression on cell membrane is good or bad for people with COVID-19 and which change in expression, if any, could make a difference.

A negative correlation between ACE2 expression and COVID-19 related morbidity and mortality has been reported in population studies, with low-risk categories (children and women) having high ACE2 levels and high-risk categories (elderly people and men) having low ACE2 levels. People over the age of 60 years are at a significantly greater risk of COVID-19. This includes an increased risk of severe illness, hospitalisation, intensive care unit admission and death (8). Therefore, when considering severity of COVID-19, the low ACE2 levels observed in elderly people and those with cardiovascular disease seem to facilitate rather than protect from the disease (9). Other aspects should be considered; in particular, in older people, the activation of the immune system may be delayed. This means that the virus can continue replicating and spreading in the body causing more extensive damage.

Several studies have evaluated the expression of ACE2 at organ and even at single cell level. A pre-print article, posted on MedRxiv, reported that gonads express high levels of ACE2 and could therefore act as a reservoir for SARS-CoV-2. The authors proposed this could be a reason for the longer duration of COVID19 in men (<https://www.medrxiv.org/content/10.1101/2020.04.16.20060566v1>). Studies investigating the expression of ACE2 at a single cell level in the heart have shown that perivascular cells, alias pericytes, that wrap coronary capillaries and arterioles, abundantly express ACE2 and hence could be a special target for SARS-CoV-2 infection in the heart (10, 11). It was suggested that patients taking ACE inhibitors should be strictly monitored because ACE inhibition can

increase ACE2 expression, thereby increasing the risk of infection. International cardiovascular societies do not consider this evidence is strong enough to stop ACE inhibitors in COVID-19 patients.

Noteworthy, the possibility that SARS-CoV-2 infects organs beside the airways is yet to be demonstrated. Although viral genetic material (viral-RNA) can be found in different organs including the myocardium, there is no substantial evidence that the virus replicates outside the lung (MedRxiv DOI: 10.1101/2020.03.05.20030502). Viral RNA in the heart may reflect killed or inactivated virus that is no longer infectious. Cardiovascular complications should be therefore reconducted to indirect effects, as also suggested by the observation that they often occur after seroconversion, that is, the transition from infection to the detectable presence of antibodies in the blood.

One indirect mechanism of cardiovascular damage in COVID-19 is represented by the induction of an exaggerated inflammatory reaction, the cytokine storm. Cytokine storms are a common complication not only of COVID-19 but of other respiratory diseases caused by coronaviruses such as SARS and MERS. They can sometimes occur in patients suffering from non-infectious diseases such as multiple sclerosis and pancreatitis. The Recovery Trial has shown that steroid treatment with low-dose dexamethasone may improve the outcome of critical patients (Clinical Trials.gov: NCT04381936)

Secondly, it is well established that there is often an association of transient production of autoantibodies with common viral infections. Autoantibodies can be induced because of cross-reactivity between viral proteins and autoantigens, molecular mimicry, and the induction of apoptosis of virus-infected cells. Another theory suggests that autoantibodies are anti-idiotypic antibodies to antiviral antibodies. Some of the commonly tested autoantibodies in viral infections include antinuclear antibodies (ANAs), antibodies directed against nucleoproteins, that is, extractable nuclear antibodies (ENA) and phospholipids, and antineutrophil cytoplasmic antibodies (ANCAs). In addition, cells of the immune system may produce antibodies specific to certain tissues or organs. Previous studies showed that autoantibodies against human epithelial cells and endothelial cells after SARS-CoV infection were responsible for SARS-induced immunopathology (12). A case report study published in the *New England Journal of Medicine* showed some severe cases of COVID-19 presented clinically significant coagulopathy, antiphospholipid antibodies, and multiple infarcts (13). The antiphospholipid syndrome is an autoimmune condition, which in the most catastrophic

variant results in multiple thromboses, organ failure and death. More research is needed on autoimmunity in COVID-19.

Finally, fragments of SARS-CoV-2, including capsid proteins, may continue to circulate in the bloodstream after virus inactivation and seroconversion. Fusion of spike protein to ACE2 would be sufficient to interfere with receptor-mediated signalling, independently of the virus. In this respect, the ACE2 hypothesis could provide an intriguing explanation not only for the path used by the virus to infect certain cells in the body but also for

the modalities by which the virus and/or viral proteins interfere with cardiovascular physiology (Fig. 1). ACE2 is responsible for the formation of vasodilator Ang 1–7, which normally opposes the action of ACE-generated Ang II. We speculate that, after engagement with the ACE2 receptor, the viral protein–ACE2 complex is internalized, leading to ACE2 degradation. As a consequence, Ang II will prevail over anti-inflammatory Ang 1–7; this imbalance resulting in activation of Ang type 1 receptor (AT1R) on vascular cells, causing vasoconstriction, vascular permeability, oxidative stress, and inflammation.

Figure 1

ACE2 downregulation by SARS-CoV-2 induces pericyte damage and microvascular dysfunction. (A) SARS-CoV-2 uses the ACE2 receptor for entry and the serine protease TMPRSS2 for S protein priming. (B) ACE2-mediated cardiovascular protection is lost following endocytosis of the receptor along with SARS-CoV-2 viral particles. (C) Unopposed ACE activity leads to Ang II generation with increased activity of angiotensin 1 receptors (AT1R) at the cost of ACE2/Ang 1–7 driven pathways. (D) This leads to increased reactive oxygen species (ROS), vasoconstriction, vascular permeability, oxidative stress, and inflammation. Moreover, ACE2 downregulation results in increased level of Des-Arg9-bradykinin (normally degraded by ACE2) which through the kinin receptor B1 (B1R) causes vascular leakage and inflammation. (E) ADAM17 mediated proteolytic cleavage of ACE2 is upregulated by endocytosed SARS-CoV-2 spike proteins. Activation of the AT1R by elevated Ang II levels also further increases ADAM17 activity. Soluble ACE2 can act as a blocking receptor for SARS-CoV-2. (F) After replication and cellular damage, the virus spreads to other cells causing incremental injury and vascular dysfunction. Alternatively, if the virus does not reach the heart, viral particles and proteins could do so, activating the described signalling pathway.

The AT1R signals through the protein kinase (MAPK) signalling pathway and phosphorylation of ADAM-17, which increases ACE2 shedding, enhancing the downregulation of ACE2 in an incremental feedback cycle.

Moreover, ACE2 is responsible for the degradation of pro-inflammatory kinin des-Arg9-bradykinin (DABK). Disruption of ACE2 could exert additional detrimental effects in COVID-19 through undegraded DABK binding to the bradykinin B1 receptor (BKB1R). An excess DABK may contribute in causing microvascular leakage, leukocyte extravasation, and pulmonary oedema in COVID-19 (<https://www.preprints.org/manuscript/202004.0023/v1>).

In conclusion, several lessons can be learnt from the COVID-19 pandemic. On the one side, researchers should not be too precipitous in reaching causative conclusions from correlative associations. On the other side, in-depth knowledge of mechanisms used by viruses to thrive and spread can lead to new treatments of viral disease, but also to novel therapeutic approaches of cardiovascular pathologies. For instance, engineered viral proteins could be used to produce specific or wide-spectrum vaccines as well as to induce or inhibit key signalling pathways implicated in cardiovascular disease.

Declaration of interest

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References

- Akhmerov A & Marban E. COVID-19 and the heart. *Circulation Research* 2020 **126** 1443–1455. (<https://doi.org/10.1161/CIRCRESAHA.120.317055>)
- Shah PB, Welt FGP, Mahmud E, Phillips A, Kleiman NS, Young MN, Sherwood M, Batchelor W, Wang DD, Davidson L, et al. Triage considerations for patients referred for structural heart disease intervention during the coronavirus disease 2019 (COVID-19) pandemic: an ACC/SCAI consensus statement. *Catheterization and Cardiovascular Intervention* 2020 In press. (<https://doi.org/10.1002/ccd.28910>)
- Patel VB, Zhong JC, Grant MB & Oudit GY. Role of the ACE2/angiotensin 1–7 axis of the renin-angiotensin system in heart failure. *Circulation Research* 2016 **118** 1313–1326. (<https://doi.org/10.1161/CIRCRESAHA.116.307708>)
- Zheng YY, Ma YT, Zhang JY & Xie X. COVID-19 and the cardiovascular system. *Nature Reviews Cardiology* 2020 **17** 259–260. (<https://doi.org/10.1038/s41569-020-0360-5>)
- Galvan Casas C, Catala A, Carretero Hernandez G, Rodriguez-Jimenez P, Fernandez Nieto D, Rodriguez-Villa Lario A, Navarro Fernandez I, Ruiz-Villaverde R, Falkenhain D, Llamas Velasco M, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. *British Journal of Dermatology* 2020 In press. (<https://doi.org/10.1111/bjd.19163>)
- Viner RM & Whittaker E. Kawasaki-like disease: emerging complication during the COVID-19 pandemic. *Lancet* 2020 **396** 1741–1743. ([https://doi.org/10.1016/S0140-6736\(20\)31129-6](https://doi.org/10.1016/S0140-6736(20)31129-6))
- Sama IE, Ravera A, Santema BT, van Goor H, Ter Maaten JM, Cleland JGF, Rienstra M, Friedrich AW, Samani NJ, Ng LL, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *European Heart Journal* 2020 **41** 1810–1817. (<https://doi.org/10.1093/eurheartj/ehaa373>)
- Osama T, Pankhania B & Majeed A. Protecting older people from COVID-19: should the United Kingdom start at age 60? *Journal of Royal Society of Medicine* 2020 **113** 169–170. (<https://doi.org/10.1177/0141076820921107>)
- AlGhatrif M, Cingolani O & Lakatta EG. The dilemma of coronavirus disease 2019, aging, and cardiovascular disease: insights from cardiovascular aging science. *JAMA Cardiology* 2020 In press. (<https://doi.org/10.1001/jamacardio.2020.1329>)
- 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. *Cardiovascular Research* 2020 **116** 1097–1100. (<https://doi.org/10.1093/cvr/cvaa078>)
- Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, Schmitt JD, Heineke J, Emrich F, Arsalan M, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. *European Heart Journal* 2020 **41** 1807–1809. (<https://doi.org/10.1093/eurheartj/ehaa410>)
- Yang YH, Huang YH, Chuang YH, Peng CM, Wang LC, Lin YT & Chiang BL. Autoantibodies against human epithelial cells and endothelial cells after severe acute respiratory syndrome (SARS)-associated coronavirus infection. *Journal of Medical Virology* 2005 **77** 1–7. (<https://doi.org/10.1002/jmv.20407>)
- Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *New England Journal of Medicine* 2020 **382** e38. (<https://doi.org/10.1056/NEJMc2007575>)

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