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Commentary

Direct or indirect endothelial damage? An unresolved question

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In this article in *EBioMedicine*, Zsuzsanna Varga and colleagues [1] published an immunohistochemistry-based study for the presence of ACE2 receptor, T-cell markers, and macrophage markers, in different anatomical regions of the coronary tree of six COVID-19 patients who died of respiratory or multiorgan failure. They found that the small heart vessels, capillaries, arterioles/venules were affected by inflammatory injury and exhibited a high density of endothelial ACE2 expression whereas the major coronary arteries were weakly or not at all affected. Interestingly, they found high ACE2 expression and an inflammatory neuropathy of the epicardial nerves, which could help to clarify the prevalence of cardiac comorbidities such as myocardial injury and arrhythmias in COVID-19.

I wish to underscore a few key points. From the first pathological studies, vascular damage and the presence of disseminated thrombotic small vessel microangiopathy appeared as typical hallmarks of severe SARS-CoV-2 infection, not only in the lung but also in the systemic circulation and several other organs distal to the lung (for a review, see [2]).

Both autoimmunity and neurotropism appear to be involved in COVID-19 neuropathies [3]. The immune-mediated injury mechanism of the myelin sheath is known as "molecular mimicry" [4]. The surface glycoproteins of the virus, against which antibodies are produced during infection, resemble neuronal glycoconjugates. For this reason, the neurons are targeted by the same antibodies, causing their injury [3]. The high expression of ACE2 in epicardial nerves found in this study, suggests the possibility of a neurotropic mechanism of SARS-CoV-2 injury. However, further studies are needed to verify the colocalization of viral RNA or spike protein with both ACE2 receptor and inflammatory markers, to unequivocally give a response to the relevant question of the direct cardiac injury.

The authors describe a major density of ACE2 receptor in capillaries and in small arterioles and venules, supporting the central role of endothelial dysfunction in COVID-19 with poor outcome and as a major determinant of virus-induced microvascular dysfunction, resulting in organ ischemia, inflammation and injury. Endothelial dysfunction plays an important pathogenic role in those patients with preexisting endothelial dysfunction due to comorbidities such as diabetes, hypertension, cardiovascular disease, obesity and cancer [5]. Therefore, they are more vulnerable to consequent endotheliitis of SARS-CoV-2 infection and have adverse outcomes. Endothelial damage can be induced both by indirect mechanisms (hypoxia, hyper-inflammatory and immune dysregulation) and by direct SARS-CoV-2 interaction to endothelial ACE2 receptor (for a review, see [2]). However, there are still some critical aspects of viral entry into cells, and tropism of SARS-CoV-2 that need further investigation. Although much has been discovered about SARS-CoV-2 cell entry, mainly its ACE2 dependence, the tissue density of ACE2 is an important but not sufficient condition to determine the infection rate of host cells. Co-localization of ACE2 and priming serine proteinases, such as TMPRSS2, is crucial for host cell entry and invasion [6]. Consistently, in the areas of histological diffuse alveolar damage, the co-expression of ACE2 protein and TMPRSS2 has been immunohistochemically demonstrated in airway cells, whereas TMPRSS2 is not detectable in endothelial cells [7]. On the other hand, another study [8] which investigated the organotropism of SARS-CoV-2 and organ inflammation in the tissues of deceased COVID-19 patients, reported that severe inflammation was limited to the pulmonary and reticuloendothelial systems and was not consistently associated with the presence of SARS-CoV-2. Analysis of 40 inflamed lung vessels did not reveal SARS-CoV-2 Spike protein within the endothelial membrane [8]. Therefore, although pathogenic studies of viral vessel injury are rapidly growing, it is not yet known whether vasculitis in COVID-19 is attributable to both direct and indirect synergistic mechanisms. The mechanisms of SARS-CoV-2 entry into cells, as well as immunohistochemical evidence of membrane-anchored virus-activating proteases which colocalize with ACE2 receptors in autoptic samples, deserve careful consideration. More in-depth research on this issue is necessary, especially considering that a higher receptor affinity or the use of a second receptor for the Spike protein of SARS-CoV-2 mutants could have awful outcomes.

Declaration of Competing Interest

The author declares no conflict of interest.

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Contributors

G. Basta wrote the commentary after a careful review of the current literature.

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