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COVID-19 as a cardiovascular disease: the potential role of chronic endothelial dysfunction

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As the SARS-CoV-2 pandemics evolves, there is mounting evidence that the cardiovascular system plays a role in the pathophysiology of COVID-19 disease. In their interesting recent article, Chen *et al.* propose that pericytes, with high expression of angiotensin-converting enzyme 2 (ACE2; the receptor for this virus), are the potential target cardiac cells for SARS-CoV-2 infection.[1] Endothelial cells are also known to express ACE2, representing a potential target for infection.[2] In addition to viral factors, other host-dependent cardiovascular factors could contribute to the severity of COVID-19 disease in some patients.

Epidemiological studies show that COVID-19 patients admitted to hospital or to an intensive care unit (ICU) present frequently with accompanying conditions such as advanced age, hypertension, diabetes, and cardiovascular diseases.[3] These conditions are associated with chronic endothelial dysfunction.[4] The endothelium plays major roles in the response to infection: endothelial cells release chemokines to guide leucocytes to the infected tissue and cytokines that activate inflammatory responses. Patients with chronic endothelial dysfunction present major alterations at the glycocalyx, intercellular junctions, and endothelial cells, resulting in enhanced leucocyte adhesion and extravasation, and also in the induction of a procoagulant and antifibrinolytic state.[4] Prior endothelial dysfunction could thus predispose to the development of severe COVID-19.

Chronic endothelial dysfunction and/or direct viral infection of endothelial cells could translate into a dysfunctional endothelial response during SARS-CoV-2 infection, which could contribute to the pathogenesis of pneumonia and acute respiratory syndrome at the respiratory level, and induce microcirculation disorders/myocardial injury in the heart, as detailed in *Figure 1*.[1] Lymphopenia and hypoalbuminaemia, which are frequent events in patients with severe COVID-19, could be explained, at least in part, by the disruption of endothelial barrier integrity at the vascular or lymphatic capillaries (*Figure 1*).[5] The dysfunctional endothelial response to the infection could also induce activation of the coagulation pathway(s), as denoted by the presence of high levels in plasma of D-dimer in severe COVID-19, which represents a risk factor for mortality.[6] It could explain the increased incidence of thrombotic complications in this disease[7] (*Figure 1*). Finally, dysfunctional endothelial responses during COVID-19 could involve not only the continuous non-fenestrated vascular endothelium (such as that present in the lungs or in the heart) (*Figure 1*), but also the continuous fenestrated endothelium (kidney) or the discontinuous/sinusoidal endothelium (liver), contributing to induction of tissue damage also at these levels.

Monitoring endothelial dysfunction biomarkers in aged patients and patients with underlying chronic diseases could help in the early identification of those individuals at risk of suffering severe complications during the course of COVID-19 illness. Designing therapies aimed to prevent endothelial deterioration and/or improve endothelial function could help improve outcomes of this disease.[8]

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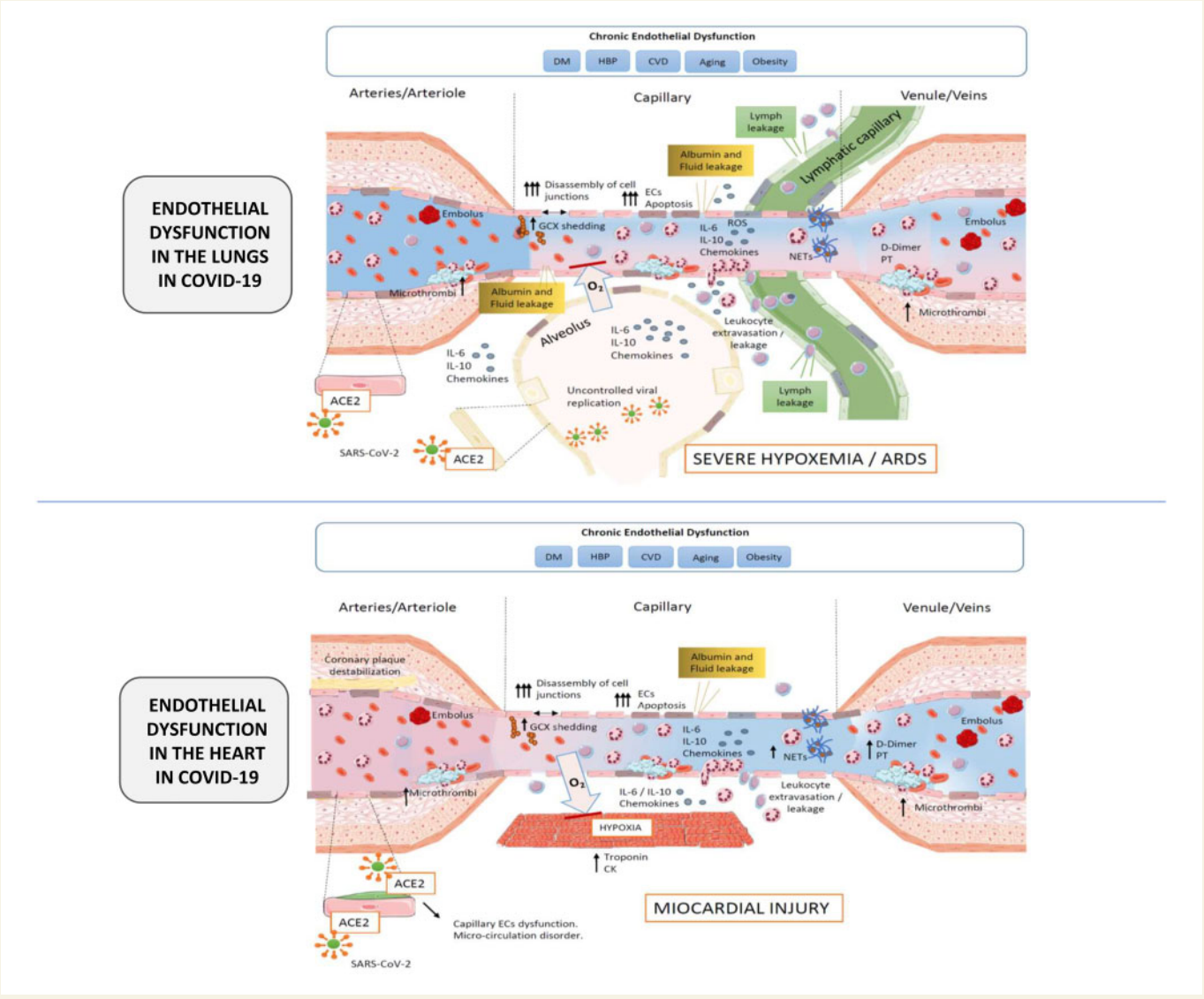

Figure 1 Endothelial dysfunction in COVID-19. In a patient unable to control the virus, viral infection could induce direct damage to the endothelial cells. Along with viral factors, the existence of prior endothelial dysfunction due to ageing and chronic diseases could favour the development of a dysfunctional response to the infection, with the production of cytokines by the patient's own endothelial cells, pneumocytes, or neutrophils, reactive oxygen species (ROS), and neutrophil extracellular traps (NETs). This dysfunctional response would translate into increased apoptosis of endothelial cells and disruption of the intercellular junctions, leading to capillary leakage of fluid, leucocytes, and proteins, which could interfere with the O_2/CO_2 exchange in the lungs and induce microcirculatory disorders in the heart. Cytokines, destabilized coronary plaque, severe hypoxia, and viral infection of pericytes (green cell in the lower panel) could also contribute to induce myocardial damage. Endothelial dysfunction would promote formation of microthrombi and emboli. Finally, dysfunction of endothelial cells in the lymphatic vessels could translate into lymphocyte leakage and lymphopenia. DM, diabetes mellitus; HBP, high blood pressure; CVD, cardiovascular disease; EC, endothelial cell; GCX, glycocalyx; PT, prothrombin time; CK, creatine kinase. Images of representative cells were taken from 'Smart Servier Medical Art' (https://smart.servier.com/).

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