Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Endothelial dysfunction in COVID-19: A potential predictor of long-COVID?

The coronavirus disease of 2019 (COVID-19) pandemic has dominated everyday life around the globe for almost two years now. While effective COVID-19 vaccines became available just about one year after the discovery of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the breakthrough in medical treatment of patients with COVID-19 is still eagerly awaited. The incomplete understanding of the multifaceted pathophysiology of COVID-19 has hampered the development of targeted therapies to date. In the current times of vaccination hesitancy and vaccine breakthrough infections, research on the pathophysiology of COVID-19 is more relevant than ever. Early studies in 2020 have demonstrated that SARS-CoV-2 targets endothelial cells making COVID-19 not only a pulmonary disease but rather a systemic vascular disease with a distinct role of endothelial dysfunction. Endothelial cells are one of the primary targets of SARS-CoV-2 due to their high expression of angiotensin converting enzyme 2 (ACE2) which has been identified as the functional receptor for SARS-CoV-2 in humans. In fact, in the year 2003 and thus long before the current COVID-19 pandemic, systemic vasculitis was identified as a main feature of SARS infection in general [1]. Few month after COVID-19 appeared, an ESC position paper emphasized the importance of endothelial dysfunction research in order to understand and treat COVID-19. Meanwhile, a growing body of evidence now suggests that SARS-CoV-2-mediated macro- and microvascular dysfunction contributes to symptoms both of acute COVID-19 illness as well as long-/post-COVID-19 syndromes.

In this issue of the *International Journal of Cardiology*, Mejía-Rentería et al. [2] report in-vivo evidence of systemic endothelial vascular dysfunction in COVID-19 by investigating the reactive hyperemia index (RHI), a measure of flow-mediated peripheral artery dilation and a surrogate of systemic endothelium-mediated vasodilative capacity, in COVID-19 patients during the acute infection and in the post-COVID stage in comparison with matched control subjects. RHI was assessed using peripheral arterial tonometry (PAT), where fingertip blood flow during reactive hyperemia following upper arm occlusion as well as under baseline conditions is measured, and the index thereof is expressed as natural logarithmic scaled RHI (LnRHI). Based on PAT assessment in the 144 study participants, systemic vascular endothelial function was found to be similar in patients with acute COVID-19 compared to controls. However, LnRHI was significantly diminished in the post-COVID-19 population compared to both the acute COVID-19 setting as well as healthy controls. Paired PAT assessments were available in a small subset of 14 COVID-19 patients during the acute and post infectious stage and were compatible with decreasing LnRHI over time from the acute COVID-19 infection to the post COVID-19 stage.

The authors of this publication from two expert groups on vascular physiology are to be congratulated for having performed this timely study that adds novel in-vivo data to the available literature on the pathophysiological role of endothelial dysfunction in COVID-19. Overall, the finding of endothelial injury in COVID-19 is in line with previous studies of COVID-19 patients both in-vivo [3,4] and post-mortem [5]. However, using a longitudinal design, the investigators were now able to gather first data on the development of endothelial dysfunction in COVID-19 over time suggesting ongoing effects of SARS-CoV-2 on human endothelial cells even after the acute infection. However, some limitations and unanswered questions associated with the study need to be considered:

First, the study by Mejía-Rentería et al. [2] has a strong focus on its primary outcome measure LnRHI while it neglects important clinical information of patients with acute-COVID (e.g. disease severity and associated complications/clinical outcomes, type of symptoms and treatments, etc.) as well as in the post-COVID population (e.g. asymptomatic vs. persistent symptoms, long-COVID, etc.) and thus fails to evaluate the potential clinical and prognostic value of PAT assessment in COVID-19.

Second, complications such as the acute respiratory distress syndrome (ARDS) in severe courses of COVID-19 infections are known to occur within the first 10 days after symptom onset in most cases [6]. Previous studies reported impaired endothelial function in patients with moderate-to-severe COVID-19 [3,4,7]. The present study by Mejía-Rentería et al. [2] performed PAT assessment on average 9.5 days after symptom onset and observed preserved endothelial function while endothelial dysfunction was only found in the post-COVID stage (PAT assessment 101 days after symptom onset), which seems contradictory to the previous studies. A potential difference in disease severity among the study populations could explain this discrepancy, but this information is missing in the present study.

Third, in contrast to the original study design that has been published at clinicaltrials.gov (NCT04525443), a historical control cohort from a different institution (Rochester, MN, USA) than the COVID-19 measurements (Madrid, Spain) were used for comparison, which - despite blinded core lab analysis - makes the data vulnerable to potential bias during data acquisition.

As previously thoughtfully summarized by Levy et al. [8], we need to keep in mind that endothelial dysfunction in systemic viral infections is neither a novel nor unique finding in COVID-19 but should be interpreted as a common road of a severe inflammatory state. Thus, whether endothelial damage is just a bystander of the severe systemic infection or a valid causal therapeutic target in COVID-19 remains to be elucidated. Notably, however, endothelial injury seen on lung autopsy of COVID-19 patients has been reported greater than in patients with ARDS from influenza [9], which should stimulate further research efforts in this

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field.

Finally, the observations by Mejía-Rentería et al. [2] may be of particular relevance with regard to long-COVID syndromes. A growing body of evidence suggests a high prevalence of long-COVID, a clinical constellation that is difficult to grasp since most routine clinical tests are inconspicuous even in highly symptomatic patients. Based on blood biomarker assessment, Fogarty et al. [10] have just recently proclaimed a potential role of persistent endotheliopathy in long-COVID. Future prospective studies combining PAT assessment with laboratory and clinical patient data will help to investigate a potential association of endothelial dysfunction with long-COVID.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

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