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Letter to the Editor

Endothelial Microvascular Dysfunction is not the only Pathophysiological Explanation for Post-acute COVID Syndrome (PACS)

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We were interested to read the article by Stahlberg *et al*. on a prospective, cross-sectional cohort study of microvascular endothelial dysfunction (MED) using the reactive hyperemia index (RHI) in 92 patients with post-acute COVID syndrome (PCAS) [1]. It was found that 41% of PCAS patients had MED and 20% had impaired RHI [1]. Patients with MED had a significant increase in pro-brain natriuretic peptide (proBNP) levels over time, and those with a greater increase in proBNP had a significantly lower RHI [1]. There was a significant correlation between the relative or absolute increase in proBNP and RHI [1]. It was concluded that peripheral MED was prevalent in a symptomatic PACS population long after recovery from a mild acute infection and that increases in proBNP levels were associated with MED [1]. The study is interesting, but several points should be discussed.

The first point is that MED is not the only pathophysiological explanation for PACS. Several other hypotheses have been proposed to explain the phenomenon. Among the most common of these other explanations for PCAS are chronic inflammation, dysregulation of the immune response (antibody-mediated overreaction of the immune system against SARS-CoV-2), persistent viral reservoirs, autonomic dysregulation, mast cell activation and neuronal abnormalities [2]. Genetic susceptibility, host immune response and viral factors likely determine the severity and duration of prolonged COVID-19 disease [2]. Some of the pathophysiological mechanisms appear to be better established than others based on prospective studies supporting them [2]. One argument against MED as a global explanation for PACS is that several manifestations of post-COVID syndrome cannot or can only with difficulty be explained by this hypothesis. For example, small fiber neuropathy (SFN), a common complication of SARS-CoV-2 infections (SC2I) or even SARS-CoV-2 vaccinations (SC2V), cannot be explained. Other common manifestations of PACS that cannot be explained by MED are autonomic dysfunction or even cerebral manifestations of PCAS.

The second point is that proBNP is not only related to microvascular endothelial function, but more often to systolic or diastolic left or right ventricular dysfunction [3]. Pro BNP is mainly produced in the left atrial appendage or left atrium, both of which are involved in extracellular and intravascular volume regulation [4]. Therefore, all patients with elevated proBNP must be screened for systolic or diastolic dysfunction by echocardiography and determination of fractional shortening or ejection fraction.

The third point is that the symptoms were taken from the patients' electronic medical records and not through direct personal contact. The disadvantage of this retrospective approach is that the documentation of patient symptoms may be insufficient or incorrect and that missing data can no longer be corrected.

The fourth point is that pulse amplitude tonometry (PAT) may depend not only on endothelial function but also on many other influencing factors, so that it would have been necessary to record all comorbidities and all concomitant medications of each included patient.

Overall, this interesting study has significant limitations that put the results and their interpretation into perspective. Addressing these limitations could strengthen the conclusions and support the message of the study. Before attributing PACS solely to MED, alternative explanations must be thoroughly ruled out. PCAS is most likely multicausal and cannot be attributed to a single mechanism.

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