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Endothelial dysfunction in COVID-19 patients assessed with Endo-PAT2000

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Abstract

It has been widely reported that the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) attaches human cells by using the Angiotensin Converting Enzyme 2 (ACE2) receptor [1], which is expressed in several organs, including the endothelial cells [2]. Whether vascular impairment described during coronavirus disease 2019 (COVID-19) infection is primarily due to the direct involvement of the endothelial cells by the virus or secondarily to the inflammatory host response is currently unknown, but there is evidence that SARS-CoV-2 can directly infect human blood vessel [3)]. Recently, Varga and colleagues, described autopsy findings from three patients who died from COVID-19, showing direct viral infection of the endothelium systemic and endotheliitis with proliferation of lymphocytes and macrophages, and loss of integrity of the endothelial monolayer [4]. These patients, however, were affected by concomitant cardiovascular disease such as hypertension, diabetes, obesity, and coronary artery disease, underlying a potential pre-existing endothelial dysfunction.

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Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Materials and Methods

We therefore aimed to demonstrate in vivo the presence of endothelial dysfunction in COVID-19 patients without cardiovascular risk factors or pre-existing cardiac conditions. We used the Endo-PAT 2000, a device able to measure endothelial vasodilation function in a rapid and non-invasive way [5]. The device records endothelium-mediated changes in the digital pulse waveform known as the Peripheral Arterial Tone (PAT) signal, measured with a pair of plethysmographic probes situated on the index finger of both patient's hands. Endothelium-mediated changes in the PAT signal are elicited by creating a downstream hyperemic response, induced by blood flow occlusion in the brachial artery for 5 minusing an inflatable cuff on one arm. The response to reactive hyperemia is evaluated automatically by the device, and a PAT ratio is calculated using the post- and pre-occlusion PAT values relative to the occluded arm (compared to the measurements from the contralateral arm, which serves as control for non-endothelial dependent systemic effects). The Reactive Hyperemia Index (RHI) is then calculated as the ratio of Pulse Wave Amplitude (PWA) measured during the 60-second period after cuff deflation divided by the average PWA measured before cuff inflation; RHI values below 1.67 are suggestive of endothelial dysfunction.

Results

We evaluated six patients with laboratory-confirmed SARS-CoV-2 infection with a mean age of 75.8 years. Five of them were female (83.3%); the average mean arterial pressure was 87 mmHg (normal values 70-110 mmHg). Blood sample tests revealed an inflammatory state in all patients, with high plasma levels of C-

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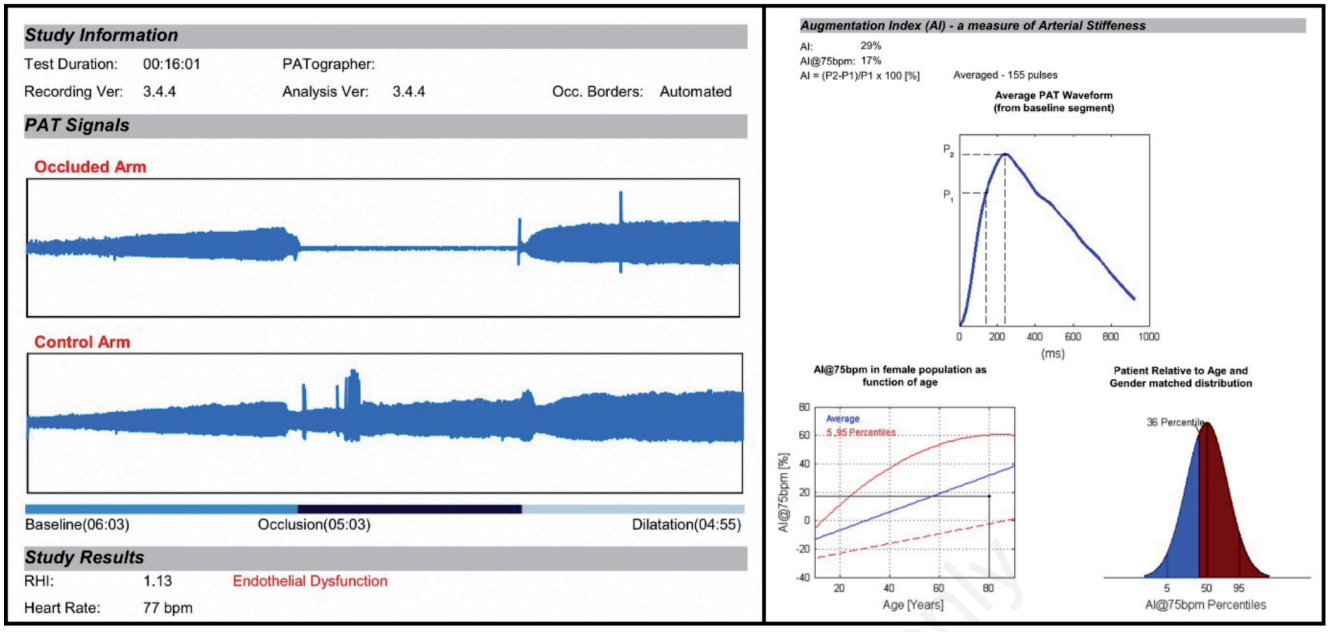

Figure 1. EndoPAT test performed on a 63-year-old female COVID-19 patient without cardiovascular risk factors or other diseases. The graph does not show any significant difference in PAT Signal increase after cuff release in the occluded arm (when compared with control arm), suggesting an endothelial dysfunction as confirmed by a RHI value well below the cutoff (1.13).

reactive protein, fibrinogen, ferritin, LDH, and D-dimer. Overall, four patients were positive for endothelial dysfunction, with RHI values between 1.13-1.56 (average value 1.32, normal values >1.67) (Figure 1); in one of the two negative patients the reported RHI value was slightly above the cutoff (1.72).

Discussion

Our findings confirm that COVID-19 patients are at higher risk of developing endothelial dysfunction. In addition, our results demonstrate that endothelial impairment may occur even in the absence of cardiovascular risk factors.

Endothelial dysfunction may play a pivotal role in the pathophysiology of the infection process and may identify a subset of patient at a higher risk of worse outcome. In a small series of patients who died from COVID-19, severe endothelial injury associated with intracellular virus detection, disruption of endothelial cell membranes, widespread pulmonary vascular thrombosis and occlusion of alveolar capillaries with significant new vessel growth, was observed [6]. Early recognition of endothelial impairment at an early stage of the disease, before the development of the mentioned histological complications, appears critical. Whether the evidence of endothelial dysfunction, through noninvasive approaches, can predict worse clinical outcomes or higher risk of thromboembolic events needs to be proven by recruiting a larger number of affected patients. Nevertheless, our results contribute to the knowledge of the pathophysiological mechanisms related to COVID-19 infection.

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