Case Report
Systemic microvascular dysfunction in COVID-19

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Abstract: COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), while having lung injury as its most prominent feature, has been increasingly shown to affect endothelial cell function and the microvasculature. In this report, a woman with COVID-19, cardiac valve disease and spherocytosis was assessed with laser Doppler perfusion monitoring. Systemic microvascular reactivity was impaired during a worsening phase of COVID-19, but improved after clinical recovery; microcirculatory dysfunction paralleled systemic inflammation and pulmonary involvement. The assessment of systemic microcirculatory function may therefore provide insights on COVID-19 pathophysiology.

Keywords: COVID-19, laser Doppler perfusion imaging, endothelial dysfunction, microvascular reactivity, cardiac valve disease

Introduction

COVID-19 is the disease caused by the seve-re acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized by a flu-like illness, evolving to a severe systemic inflammatory syndrome in 5 to 15% of those affected [1-3]. Lung injury with hypoxemia is the most prominent feature, and may lead to the need for supplementary oxygen or even mechanical ventilation. Mortality is higher among those over 60 and those with diabetes, hypertension, cardiovascular disease, chronic kidney disease, chronic pulmonary disease, liver disease and obesity [1, 2]. Pathophysiology is not fully understood but endothelial cell dysfunction plays a major role [4], and few treatment resources have proven effective [5, 6]. Steroids have recently been shown to be beneficial in those with moderate to severe forms of the disease [7]. Herein we describe a case of severe microcirculatory dysfunction in a patient with valvular heart disease and COVID-19.

Case report

A 32-year-old woman with a history of rheumatic valve disease, metallic prosthetic valves in the mitral and aortic positions (three prior valve replacement surgeries), a cardiac pacemaker implant for complete heart block, and hereditary spherocytosis, was evaluated at the Cardiology outpatient clinic due to mild shortness of breath, fever (38.5°C), rhinorrhea and dry cough in the previous five days. Her ECG showed pacemaker rhythm, heart rate of 80 bpm, with left bundle branch block pattern and a ventricular spike. The corrected QT interval was of 430 msec. The echocardiogram showed left atrial enlargement, mild systolic left ventricular dysfunction (left ventricular ejection fraction of 48% by the Simpson method), and normally functioning mitral and aortic prostheses. After a chest CT (**Figure 1A**) was obtainedand a nasopharyngeal swab for RT-PCR of SARS-Cov2 was collected, oral azythromicin and amoxycilin + clavulanate were started, and the patient was discharged, with instructions for clinical monitoring.

After three days (on day 8 after the beginning of symptoms), she returned for emergency evaluation due to bloody sputum, diarrhea and increased dyspnea. The nasopharyngeal swab was positive and COVID-19 was diagnosed. Chest CT (**Figure 1B**) showed a worsening pattern of viral pneumonia, and C-reactive protein (CRP) was 29 mg/dL. The patient was admitted and amoxycilin + clavulanate was changed to ceftriaxone. Azythromicin was maintained, and
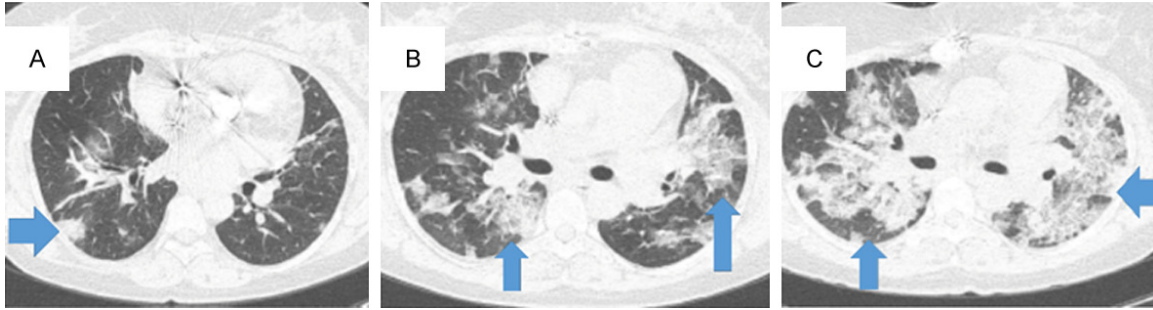
Figure 1. Chest CT images performed on three different moments of clinical evolution. A: Outpatient study, showing bilateral, rounded foci of consolidation and ground-glass images, in <50% of the lung fields. B: At admission, showing bilateral consolidations and ground-glass images, occupying >50% of the lung fields. C: On the worst day after admission, with an increase of the ground-glass opacities, which became confluent and associated with interlobular septal thickening and bilateral consolidation. Arrows point out some of the pulmonary lesions of the patient.
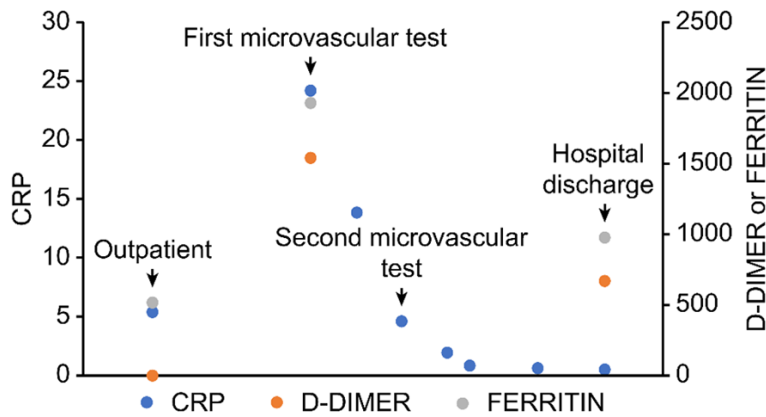

Figure 2. Evolution of C-reactive protein (CRP, mg/dL), d-dimer (ng/mL) and ferritin (μg/L) serum levels.

The patient improved on the following days: she became afebrile on the 16th day after the onset of symptoms, and was weaned from supplemental oxygen. CRP decreased to 4.4 mg/dL (**Figure 2**).

The evaluation of microvascular flow and reactivity was performed on two different occasions, the first on day 12 (when the patient presented the worst clinical features since hospital admission) and the second on day 16 (after clinical and laboratory improvement). Endothelium-dependent vasodilation of skin microcirculation was evaluated using a single-point laser doppler perfusion monitoring (LDPM) system (Periflux 5001, Perimed, Järfälla, Sweden), for noninvasive measurement of systemic microvascular perfusion changes (in arbitrary perfusion units [APU = 10 mV]), as previously described [8, 9]. After measuring the resting microvascular flow on the skin of the forearm, the maximal microvascular vasodilatation was assessed using prolonged (20 minutes) local heating of the laser probe to 44°C (local thermal hyperemia, LTH) (**Figure 3**).

This case report is part of a prospective study, which investigates systemic microvascular flow and reactivity in patients in the acute phase of COVID-19. The study was approved by the Institutional Review Board (IRB) of the National Institute of Cardiology and was registered and

oseltamivir was added to the therapeutic regimen. Warfarin (used chronically) was changed to full-dose IV heparine, and oxygen therapy was delivered by face mask.

On the following four days, the patient required increasing oxygen concentrations, and had persisting fever and worsening dyspnea, with tachypnea (44 breaths/min). CRP was elevated (24.2 mg/dL), as well as ferritin (1,930 μg/L), and d-dimer (154,000 ng/mL); the chest CT also showed deterioration (**Figure 1C**). Blood cultures were negative. Piperacillin + tazobactam and IV methylprednisolone were initiated; oseltamivir, ceftriaxone and azythromicin were stopped (the latter due to QT interval prolongation). High-flux continuous supplemental oxygen maintained saturation at 97%, and mechanical ventilation was not necessary.
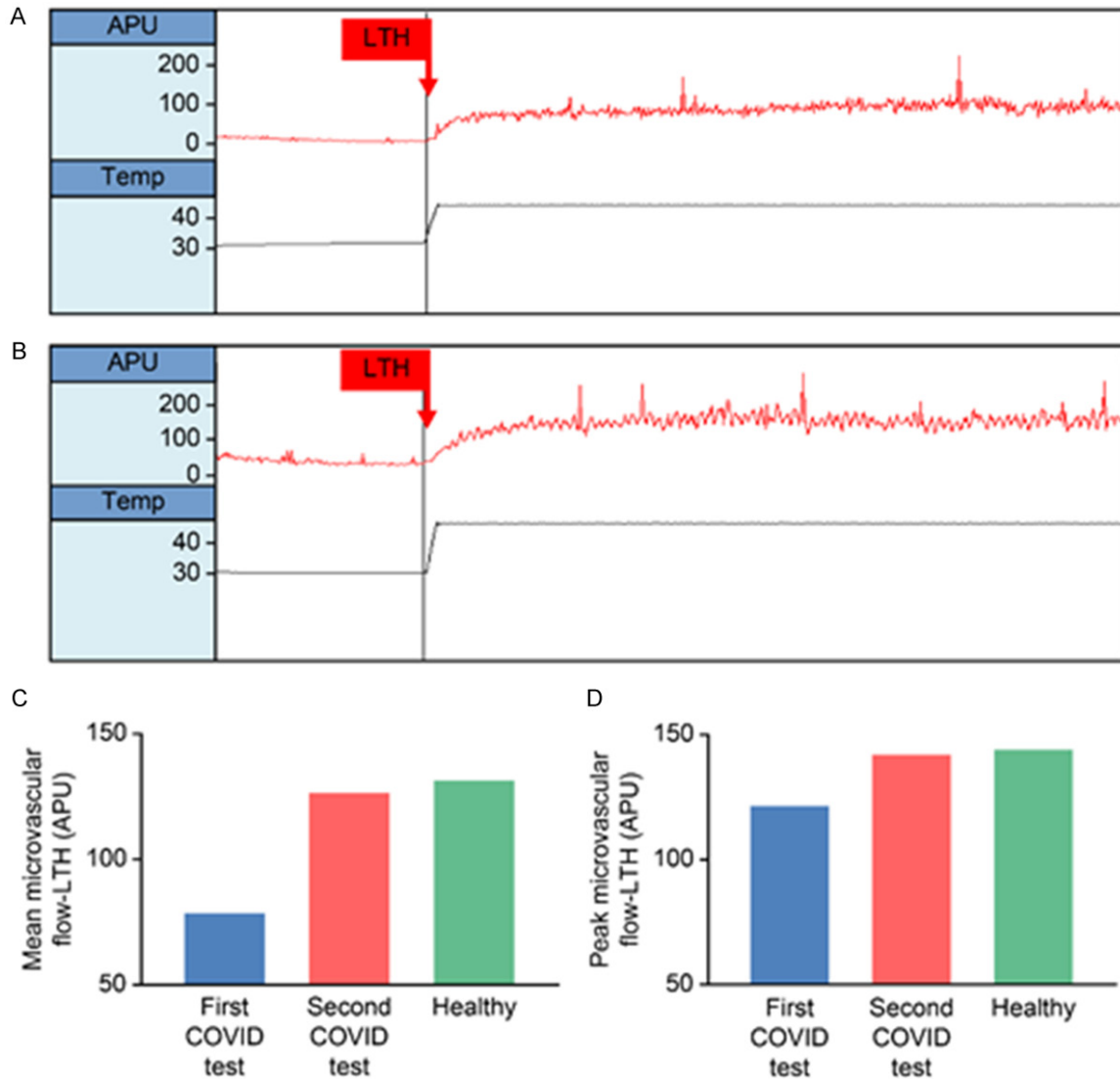
Figure 3. Upper panels: Recordings of skin microvascular flow using laser doppler perfusion monitoring, with local thermal hyperemia (LTH) stimulus. (A) Patient with COVID-19, first test (worst day during clinical evolution). (B) Same patient, second test, after clinical and laboratory improvement. There is higher baseline flow, as well as post-LTH flow on the second test. Lower panels: Bar graphs showing the effect of LTH on mean (C) and peak (D) cutaneous microvascular flow of the patient, in the first test (blue bars) and on the second test (red bars), compared to a sex- and age-matched healthy control (green bars). APU, arbitrary perfusion units; LTH, start of local thermal hyperemia; TEMP, skin temperature.

made public at ClinicalTrials.gov (NCT44065-45). The subject included in this case report read and signed the informed consent form approved by the IRB before inclusion.

Discussion

An association between the presence of cardiovascular disease or myocardial injury and adverse prognosis has been demonstrated in patients with COVID-19, with increases of up to 10 times in mortality [10, 11]. As an initial process, SARS-CoV-2 virus, anchored in the transmembrane angiotensin-converting enzyme 2 (ECA2) receptor, penetrates host cells, including endothelial cells [12, 13]. The ensuing endothelial dysfunction may contribute-together with the chronic endothelial dysfunction present incomorbidities such as hypertension, diabetes, coronary artery disease and obesity [14, 15]- to more severe presentations, faster evolution and worse outcomes.

Table 1. Summary of the case report

Case description	A 32-year-old woman with cardiac valve disease and spherocytosis, diagnosed with COVID-19. Systemic microvascular reactivity assessed with cutaneous laser doppler perfusion monitoring, with thermal hyperemia
First microcirculation test	Performed in the worst day of clinical evolution-severely impaired microvascular vasodilation, compared to a healthy control
Second microcirculation test	Performed after clinical and laboratory improvement-marked increase in baseline microvascular flow and endothelial-dependent vasodilation

The cutaneous microcirculation is an accessible and representative vascular bed for the evaluation of systemic microcirculatory flow and reactivity [16]. LDPM, which was employed in this study, is a noninvasive method for the evaluation of systemic microvascular endothelial function in diverse clinical or surgical conditions [9, 17, 18]. The skin vasodilatory response resulting from LTH assesses microvascular function and reactivity, and consists of a biphasic response. The initial peak mediated by a calcitonin gene-related peptide, dependent on the axonal reflex of the sensory nerves, is followed by long-term plateau phase, mediated primarily by substances produced by the vascular endothelium, such as nitric oxide and hyperpolarizing factors derived from the endothelium [8].

In this patient, systemic endothelium-dependent microvascular reactivity was severely impaired on day 12, but recovered to levels similar to those of a sex- and age-matched healthy control on day 16 (**Figure 2**). Both resting microvascular flow, as well as mean and peak flows during LTH, were higher in the second test, when the patient was improved (**Table 1**). These changes occurred in parallel with improvements of CRP. This biomarker is increased in patients with COVID-19, most likely due to systemic inflammation [19, 20]. Systemic inflammation may account for endothelial function abnormalities [21], as endothelial cells and microvascular function are known to be affected by circulating inflammatory cytokines and reactive oxygen species, for example, which are increased in sepsis- the release of inflammatory mediators and reactive molecules to destroy pathogens may ultimately cause endothelial damage [22, 23].

Bearing in mind that the presence and intensity of systemic microvascular changes during the acute phase of COVID-19 may be related to disease progression and prognosis, the impor-tance of the evaluation of microvascular reactivity in these patients should be underscored. To the best of our knowledge, this is the first report on the detrimental effect of COVID-19 on endothelium-dependent systemic microvascular reactivity in human beings. The current findings may point towards a unique opportunity for further evaluation of the microcirculation in this patient population, with a fast, simple and noninvasive method.

Conclusions

Systemic microvascular dysfunction may occur in patients with COVID-19, paralleling the inflammatory status of the disease. Laser doppler perfusion monitoring with local thermal hyperemia on the skin may be valuable to noninvasively evaluate the systemic microcirculation in COVID-19, offering useful information, which may have therapeutic and prognostic implications.

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Disclosure of conflict of interest

None.

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