Recovery of Endothelium-dependent vascular relaxation impairment in convalescent COVID-19 patients: Insight from a pilot study

Fares Gouzi, Aurélien Philippe, Jean Pastre, Bertrand Renaud, Nicolas Gendron, Marielle Subileau, Thông Hua-Huy, Benjamin Planquette, Olivier Sanchez, David Smadja, et al.

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FaresGouzia,b,AurélienPhilippeb,c,JeanPastred,BertrandRenaude,f,NicolasGendronb,c,MarielleSubileaue,ThongHuaHuye,BenjaminPlanquetteb,e,OlivierSanchezb,e,DavidM.Smadjab,c,1, SvenGûntherb,e,*,1

a PhyMedExp ,INSERM-CNRS Montpellier University, CHRU Montpellier, Montpellier, France

b Université Paris Cité, Innovative Therapies in Haemostasis, INSERM UMR_S1140, ParisCité,F-75006 Paris, France

c Hematology Department, AP-HP, Georges Pompidou European Hospital, F-75015 Paris, France

d Department of Respiratory Medicine, AP-HP, Georges Pompidou European Hospital F-75015 Paris, France

e Unité d'Explorations Fonctionnelles Respiratoires et du Sommeil, AP-HP, Georges Pompidou European Hospital, F-75015 Paris, France

f Université Paris Cité, U FR de médecine,F-75006 Paris, France

Keywords:

SARS-CoV-2, infection, Endothelial dysfunction, Endothelial damage, Reactive hyperaemia index

Abbreviations:

Ang, angiopoietin; ATS, American Thoracic Society; BMI, body mass index; BP,bloodpressure;CT,computedtomography;DLCO,diffusingcapacityofthe lung for carbon-monoxide ;ERS, European Respiratory Society; FMD, flow-mediated dilation; FRC,functionalresidualcapacity;HAD-S,hospitalanxietyanddepression scale; MRC, medical research council; 6-MWD, 6-minute walk distance; PAT, peripheral arterial tone; PFT, pulmonary function test; RHI, reactive hyperaemia index; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2;SD, standard deviation; TCO, transfer factor for carbonmonoxide; TLC, total lung capacity; WHO, World Health organization

*** Corresponding author at**:

Innovative Therapies in Haemostasis, INSERM UMR_S1140, Paris Cité University, F-75006 Paris, France.

E-mail address: sven.gunther@aphp.fr (S. Gûnther).

1 Both authors contributed equally to this study.

ABSTRACT

Background:

Endothelial dysfunction is a key-feature in acute COVID-19. However, follow-up data regarding endothelial dysfunction and injury after COVID-19 infection are lacking. We aimed to investigate the changes in endothelium-dependent vasorelaxation at baseline and four months after hospital discharge in COVID-19 patients.

Methods:

Twenty COVID-19 patients were compared to 24 healthy controls. Clinical and morphological data were collected after hospital admission for SARS-CoV-2 infection and reactive hyperaemia index (RHI) measurement was performed with a delay between 24 and 48h after hospital admission and four months after hospital discharge in the out patient clinics. Blood tests including inflammatory markers and measurement of post-occlusive vasorelaxation by digital peripheral arterialonometry were performed at both visits.

Results:

At baseline, COVID-19 patients exhibited reduced RHI compared to controls ($p<0.001$), in line with an endothelial dysfunction. At four months follow-up, there was a 51% increase in the RHI (1.69+/-0.32 to 2.51+/-0.91; $p<0.01$) in favor of endothelium-dependent vascular relaxation recovery. RHI changes were positively correlated with baseline C-reactive protein ($r=0.68$;$p=0.02$).Compared to COVID-19 patients with a decrease in RHI, COVID-19 patients with an increase in RHI beyond the day-to-day variability (i.e.>11%) had less severe systemic inflammation at baseline .

Conclusion:

Convalescent COVID-19 patients showed a recovery of systemic artery endothelial dysfunction, in particular patients with lower inflammation at baseline. Further studies are needed to decipher the interplay between inflammation and endothelial dysfunction in COVID-19 patients.

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1. Introduction

COVID-19, caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), is associated with systemic vascular disease [1]. Endothelium dysfunction has been documented in postmortem studies [2,3]. In the acute phase of disease, increased plasma endothelial markers as well as circulating endothelial cells (CEC) – a marker of an endothelial injury – have been reported [4,5]. The vascular impairment is not limited to the pulmonary circulation [6–8] and endothelial dysfunction in the systemic circulation has been demonstrated by assessing endothelium-dependent vasorelaxation [9,10]. The role of inflammation in the setting of COVID-19 infection is discussed because it is supposed that the crosstalk between platelets, the coagulation system and the endothelium in inflammatory conditions is perturbed and may even exacerbate the inflammatory process. The association of inflammatory stress and underlying cardiovascular diseases may therefore lead to endothelial dysfunction [11,12], resulting to an altered post-occlusive vasorelaxation.

The endothelial and vascular impairment could persist after the acute phase. Indeed, more than 12 weeks after SARS-COV-2 infection [13], cardiovascular complications including labile heart rate and blood pressure (BP) responses, myocarditis/pericarditis, impaired myocardial flow reserve and arrhythmias [14] have been reported in patients with persistent unexplained clinical symptoms (dyspnea, asthenia, mood disorders, ...). Moreover, one follow-up study in convalescent COVID-19 patients has reported that the endothelium-dependent vasorelaxation decreased 80 days after the COVID-19 infection [15]. Yet, these patients have not been characterised in terms of determinants of endothelial dysfunction (physical activity) or endothelial injury. Therefore, recovery of endothelium-dependent dysfunction could remain incomplete in convalescent COVID-19 patients. Moreover, the time-course of endothelial function/injury could be heterogeneous in post-COVID-19, with different phenotypes between patients in whom endothelial function will be recovered and those who will not recover.

The aim of this study was to assess the changes in endothelium-dependent vasorelaxation in patients hospitalised for SARS CoV-2 infection, at hospital admission and four months after discharge. The study also compared the clinical, vascular and pulmonary function characteristics four months after hospital discharge between patients who improved their post-ischemic peripheral vasorelaxation and those who did not.

2. Methods

2.1. Participants, setting and design

Adult patients admitted to the Department of Respiratory Medicine at the European Georges Pompidou Hospital, Paris, France, from 1 February to 2 June 2021, with a positive reverse-transcriptase-polymerase chain reaction on a nasopharyngeal swab and subsequently discharge alive, were eligible. All patients provided written informed consent.

Patient interviews, standardised reviews of medical records and assessments were performed during the first visit at baseline and the second scheduled visit at least 12 weeks after hospital discharge. The severity of COVID-19 during hospitalization was defined according to the World Health organization (WHO) into: (i) mild to moderate (non-severe); (ii) severe; and (iii) critical (defined by the criteria of acute respiratory distress syndrome, sepsis, septic shock, or other conditions requiring life-sustaining therapies such as non-invasive ventilation or mechanical ventilation). Demographic (age, sex), morphologic (height, weight) and clinical characteristics including the dyspnea score (Medical Research Council (MRC) scale) [16], cough, asthenia, myalgia, chest pain, and underlying cardiovascular comorbidities and/or respiratory comorbidities were assessed during baseline and follow-up visits. The severity of the pulmonary impairment assessed by chest computed tomography (CT) scans according to the standardised 0–4 score (0: no involvement; 1: <25% involvement; 2: 25–50% involvement; 3: 50–75% involvement; 4: >75% involvement) [17] was assessed at baseline. Blood tests and non-invasive measurement of peripheral arterial tone (PAT) reflecting endothelial function were performed during both visits. During the second visit, patients completed a standardised set of questionnaires and performed pulmonary function tests.

2.2. Ethics rules

The institutional review board from the scientific and ethical committee of the Assistance Publique-Hôpitaux de Paris approved the present study (No. CPP 2020-04-048b/2020-A01048-31/20.04.21.49318) and the patients were included in the study entitled "EnDOthelial coagulopathy as a predictor of the severity of SARS-CoV-2 infection – SARCODO" (NCT04624997).

2.3. Post-occlusive vasorelaxation by measuring PAT

Endothelium-mediated vasoreactivity was evaluated at baseline and during follow-up using the digital plethysmography system, EndoPAT2000® (Itamar Medical, Caesarea, Israel). This devise allows the non-invasive recording of the arterial tone of the peripheral arterial bed, a technology which is non-operator-dependent. The PAT® signal is measured by fingertip plethysmography. This devise records changes in digital volumes under the effect of the arterial pulse after occlusion of the brachial artery according to the recommendations of the International Brachial Reactivity Task Force [18]. This measure has the advantage of integrating *de facto* contralateral control when assessing post-occlusive reactive hyperaemia on an arm, to overcome the effect of endothelium-independent systemic factors on vascular tone [19,20]. The reactive hyperaemia index (RHI) is calculated using the following formula:

$$RHI = \frac{DH_{PO}}{DH_{BASE}} \Big/ \frac{DC_{PO}}{DC_{BASE}}$$

where DH = hyperaemic finger pulse range; DC = finger pulse range control; BASE = pre-occlusion; PO = post-occlusion.

The EndoPAT 2000® provides a measure of the RHI, which reflects the endothelial function of medium and small arteries of the upper limbs. The RHI has been explored in previous studies as an endothelium-dependent measurement [21] and the RHI has been validated as an indicator of endothelial (dys-)function in incident cardiovascular events in older individuals [22]. This has been validated versus the reference method in healthy subjects and subjects at vascular risk [23]. Endothelium-dependent vasorelaxation appears to be sensitive to various interventions in chronic obstructive pulmonary diseases [24]. The procedure was standardised in the Framingham Heart Study [19,20] and measurements in our study were performed as recommended [20,25]. RHI values <1.67 are suggestive of underlying endothelial dysfunction. Given the published day-to-day variability of the RHI [26], a RHI improvement of >11% was defined for patients with an improvement of their endothelium-dependent vasorelaxation [26].

2.4. Lung function testing

Pulmonary function tests (PFTs) included spirometry, functional residual capacity (FRC), total lung capacity (TLC) and the diffusing capacity for carbon monoxide (DLCO) by single breath real-time CO/NH_4 measurements. FRC was measured by body plethysmography (Vyntus Body, DUOMED, Flaxlanden, France). Predicted values from the Global Lung Function Initiative (GLI) were used for forced vital capacity and DLCO [27,28]. PFT findings were considered to be abnormal when <80% of the predicted value. A 6-minute walking distance (6-MWD) test was performed according to ATS/ERS recommendations [29]. The results were expressed as metres and % of predicted values were calculated using a method described by Enright et al. in 1998 [30].

2.5. Questionnaires

Mood disorders including anxiety and depression were assessed during follow-up using the Hospital Anxiety and Depression Scale (HAD-S). A score of <7 indicated the lack of significant symptoms, while a score of >11 indicated obvious symptoms [31]. Physical activity level was evaluated with the Voorrips questionnaire. A score of <9.4 indicates a low level of physical activity [32].

2.6. Statistical analysis

All continuous variables were tested and are expressed as mean ± standard deviation (SD) if normally distributed, or as median [interquartile range: 25–75%] if not. Baseline comparisons between healthy controls and COVID-19 patients were made using the Student's *t*-test (normally distributed variables) or the Mann–Whitney *U* test (non-normal distribution) for continuous variables and Fisher's exact test for categorical variables. Changes between the first and second visits were assessed using paired t-tests (normally distributed variables) or the Wilcoxon test (non-normal distribution). Correlations were assessed using Pearson's coefficients. Results were statistically significant at $p < 0.05$. Statistical analyses were performed using GraphPad Prism 5 version 5.02.

3. Results

3.1. Study population

Twenty COVID-19 patients were admitted to the Department of Respiratory Medicine. A history of hypertension, dyslipidaemia, diabetes mellitus or tobacco smoking was found in 30%, 20%, 10% and 50% of patients, respectively. At admission, all patients showed evidence of systemic inflammation with increased C-reactive protein (113 ± 59 mg/L), white blood cells and neutrophils (9.08 ± 4.56 x 10^7/mm^3 and 7.54 ± 4.14 x 10^7/mm^3, respectively) and D-dimer (1444 ± 946 μg/L). A first visit was performed 14.7 ± 7.4 days after symptom appearance in favor of SARS-CoV-2 infection and assessment of endothelial function by PAT has been carried out. According to the WHO definition, patients were equally distributed between severe (50%) and critical (50%) disease patients with signs of respiratory failure. Pulse oximetry at admission indicated hypoxemia with SpO_2 = 86 ± 1%, and all patients required oxygen therapy. Two patients (10%) needed non-invasive ventilation and three patients (15%) invasive mechanical ventilation. Regarding vascular therapies, 95% of patients were administered anticoagulation (60% preventive/30% curative) and 95% of patients received oral corticosteroids. Specific anti-SARS-CoV-2 therapy was administrated to 25% of patients. One patient died 28 days after hospital admission. The demographic, clinical and functional characteristics of the COVID-19 patients are summarised in Table 1 along with the characteristics of a population of stable healthy controls that were matched for age and underwent a similar assessment procedure.

3.2. Assessment of vasorelaxation

Brachial endothelium-dependent vasorelaxation was impaired in COVID-19 patients, as shown by a 34% reduction in the RHI (Fig. 1). Using the RHI cut-off of 1.67, 8/20 (40%) of the COVID-19 patients showed an endothelial dysfunction, while the endothelial function was normal in all healthy controls. Among the 20 COVID-19 patients, a subgroup of 12 patients had a follow-up of 123 ± 58 days after baseline assessment during the acute phase of COVID-19 infection. Baseline RHI in this subgroup did not differ significantly from the whole COVID-19 population (1.85 ± 0.09 vs. 1.69 ± 0.09; $p = 0.27$). Forty percent of these COVID-19 patients reported persistent functional symptoms after COVID-19 infection, mainly represented by a modified (m)MRC dyspnea score = 2.10 ± 0.70. These patients showed limited pulmonary fibrosis sequelae (TLC: 93.2 ± 11.9% predicted) and transfer factor for carbon monoxide (TLCO): 70.0 ± 14% predicted. All patients had a low level of physical activity evaluated by a Voorrips score <9.4 (6.29 ± 6.01). Although surprisingly symptoms of anxiety or depression were limited (HAD-S scale: A: 6.8 ± 4.2 and D: 4.4 ± 2.8), with an anxiety score of >11 in 40% of patients. At four months follow-up, there was a 51% increase in the RHI (1.69 ± 0.32 to 2.51 ± 0.91; $p < 0.01$) (Fig. 2); in favor of recovery of endothelium-dependent vascular relaxation. The RHI difference between COVID-19 patients and healthy controls was no more significant (2.51 ± 0.26 vs. 2.86 ± 0.11; $p = 0.24$) and only 2 /12 patients showed a RHI <1.67. No significant improvement in BP was observed (diastolic BP: 75.3 ± 13.2 to 79.1 ± 9.6, $p = 0.50$; systolic BP: 119.1 ± 25.3 to 126.8 ± 11.5, $p = 0.42$).

Considering a threshold of a RHI improvement of >11%, five COVID-19 patients were classified as "non-improvers" and seven patients as "improvers". The differences in "non-improvers" vs. "improvers" between baseline and follow-up visits are reported in Tables 2 and 3, respectively. No difference in pre-existing cardiovascular disease was observed between "non-improvers" and "improvers". COVID-19 patients who had a recovery of their endothelium-dependent vascular relaxation had a lower BP and C-reactive protein at baseline. Moreover, significant and positive correlations were found between baseline C-reactive protein and RHI change after four month ($r = 0.68$; $p = 0.02$) and between baseline blood leukocytes and RHI change after four month ($r = 0.61$; $p = 0.03$).

Table 1
Characteristic of the COVID-19 patients and healthy controls at the first assessment.

	Healthy controls (n = 24)	COVID-19 patients (n = 20)	P value
Age (years)	55.8 ± 11.6	56.8 ± 11.5	0.61
Sex ratio (F/M)	12/12	4/16	<0.05
BMI (kg/m^2)	24.2 ± 2.9	29.7 ± 5.7	<0.01
History of hypertension	0 (0%)	6 (30%)	
Tobacco smoke (pack/years)	1.9 ± 4.7	27.5 ± 8.5	<0.001
Never/former/ current smoker	19/2/3	10/9/1	0.019
Diastolic BP (mmHg)	80.92 ± 1.43	74.72 ± 2.68	<0.05
Systolic BP (mmHg)	128.8 ± 2.83	121.1 ± 4.67	0.14
Heart rate (/min)	68.63 ± 2.25	78.40 ± 2.91	<0.01
Leukocytes (10^7/ mm^3)	5.22 ± 1.17	9.30 ± 4.00	<0.001
Reactive Hyperaemia Index (%)	2.80 ± 0.11	1.85 ± 0.10	<0.001

Values shown are mean ± SD, or n (%).
F: female; M: male; BMI: body mass index; BP: blood pressure; SD: standard deviation.

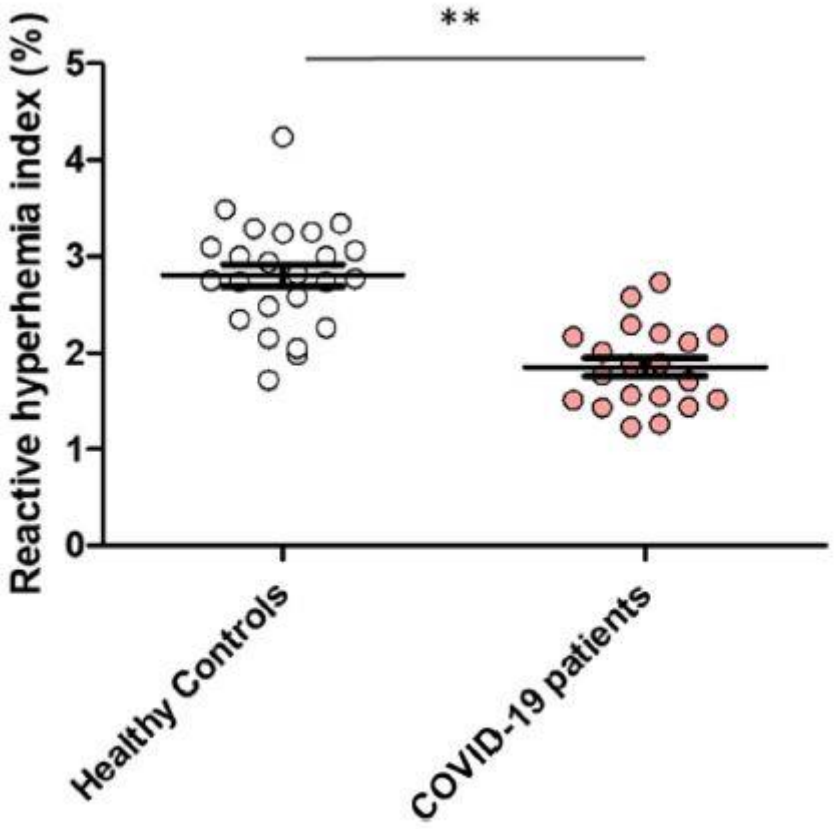

Fig. 1. Reactive hyperaemia index (%) assessed by post-occlusive pulse arterial tonometry in healthy controls and COVID-19 patients at the first assessment. **p<0.001.

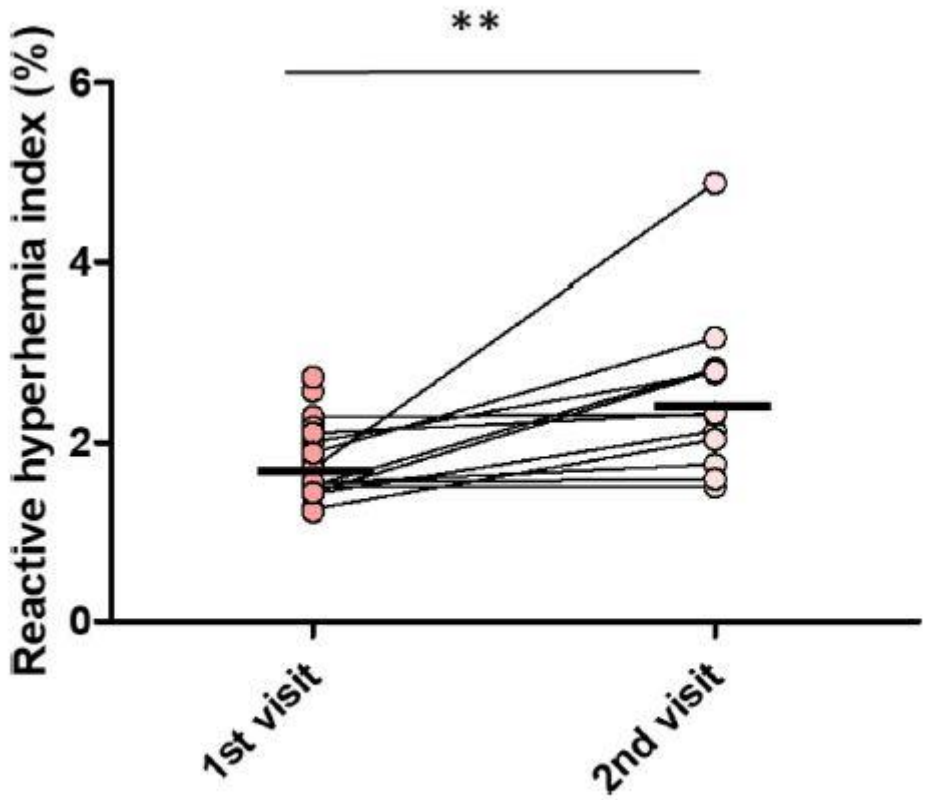

Fig. 2. Reactive hyperaemia index in the first and second visit (%) in COVID-19 patients. (A) Black bar represent median. $^{**}p<0.01$.

4. Discussion

In this pilot study concerning convalescent COVID-19 patients, we found a significant recovery of endothelium-dependent vasorelaxation after four months of follow-up, which contrasts with previous studies. However, patients with higher inflammatory state at admission during acute phase of SARS CoV-2 infection are those with incomplete recovery.

In the acute phase, COVID-19 patients with severe pulmonary lesion on CT scans showed a reduction in RHI versus healthy controls.

This RHI reduction indicated an impairment of endothelium-dependent vasorelaxation, in line with results from a meta-analysis using the brachial flow-mediated dilation (FMD) method [33]. Moreover, the RHI was <1.67 in 40% of COVID-19 patients, indicating an endothelial dysfunction. Yet, this endothelial dysfunction could be the consequence of the cardiovascular diseases reported in our COVID-19 patients [34]. In fact, when compared to healthy controls matched for age, sex, body mass index (BMI) and underlying cardiovascular diseases (hypertension), Mejia-Renteria et al. showed no different RHI between COVID-19 patients and healthy controls [15]. Thus, the magnitude of the endothelial injury at the acute phase of COVID-19 confirms the role of the acute disease on the vascular endothelium, even though pre-existing cardiovascular disease, smoking habits and vasoactive medications could constitute a susceptibility factor.

Four months after SARS-CoV-2 infection, our COVID-19 patients showed a significant RHI improvement. These results are in contrast to the only study published to date in COVID-19 patients [15], which reported a 42% reduction in RHI 80 days after SARS-CoV-2 infection (n = 14). Interestingly, the initial natural log transformation of RHI was 19% higher than in our study (0.59 ± 0.23). Unfortunately, the lack of a full report of disease severity and treatments does not allow us to further speculate about observed discrepancies. In addition, the improvement in endothelial dysfunction is also in line with evidence of a recovery of vascular function in COVID-19 patients, such as arterial stiffness [8]. Last, an improvement in the skin microvascular flow during local thermal heating 12–15 weeks after infection has been reported [35] which suggests an improvement in vascular reactivity in COVID-19 patients. Altogether, our study argues for a reversibility of the deleterious effect of COVID-19 on the systemic endothelium [1], which is in line with the transient deleterious effect of an acute infection reported on the endothelial function, whether respiratory [36] or not respiratory [37].

In our subgroup analysis, the RHI improvement occurred in patients with less systemic inflammation at admission (reduced C-reactive protein, lower blood leukocytes and neutrophils), meaning that the severity of the initial inflammatory syndrome was associated with the lack of recovery of endothelial dysfunction. The role of the

systemic inflammation at the acute phase of COVID-19 is highlighted by the significant correlations between the RHI and the baseline C-reactive protein, meaning that the less the acute inflammation, the more the endothelial dysfunction and injury recovers [12]. Here again, this result cannot be explained by a pre-existing vascular comorbidity and confirms the role of the infection on endothelial dysfunction in COVID-19 patients [12]. Moreover, relationship between initial inflammation and endothelial dysfunction is in line with Pr Randi's data indicating that direct endothelial infection by SARS-CoV-2 is not likely to occur; however the endothelial could be rather related to inflammation [1,38]. Indeed, the cytopathic effect was correlated with the level of plasma inflammatory cytokines, which suggests the possible cytotoxicity of cytokines such as IL-6, IL-1β, and tumor necrosis factor−α on endothelial cells [39], through apoptosis [40].

Table 2
Baseline comparisons between COVID-19 patients who did not improve ($n = 5$) and patients who improved ($n = 7$) their RHI between the first and second visit.

	No improvement in RHI ($n = 5$)	Improved RHI ($n = 7$)	*P* value
Age (years)	54.8 ± 9.0	56.7 ± 10.5	0.75
Sex ratio (F/M)	1/4	3/4	
BMI (kg/m^2)	27.2 ± 3.1	29.6 ± 4.5	0.33
Tobacco smoking (pack/years)	22.5 ± 3.5	28.8 ± 8.5	0.40
Charlson Comorbidity Index	0.80 ± 0.37	2.00 ± 0.93	0.32
History of hypertension (n/patient)	0.0 [0.0–1.0]	0.0 [0.0–0.5]	0.83
Time from appearance of first symptoms (days)	12.4 ± 7.1	10.9 ± 5.2	0.67
Admission in ICU (n)	2	2	1.00
Chest CT scan severity score (/4)	3.0 ± 0.8	2.2 ± 1.5	0.34
SpO_2 room air (%)	86.8 ± 4.5	86.7 ± 2.1	0.98
Respiratory rate (/min)	21.5 ± 4.4	21.7 ± 7.4	0.97
leukocytes (10^7/mm^3)	13.5 ± 5.3	8.4 ± 4.5	0.10
Hemoglobin (g/dl)	12.9 ± 2.2	14.5 ± 1.2	0.12
Platelets (/mm^3)	317 ± 131	259 ± 109	0.42
Neutrophils (10^7/mm^3)	11.4 ± 5.1	6.9 ± 3.8	0.11
Lymphocytes (10^7/mm^3)	1.2 ± 0.3	0.9 ± 0.6	0.33
D-dimer (μg/L)	1537 ± 433	2168 ± 1169	0.28
C-reactive protein (mg/L)	157 ± 60	80 ± 54	0.05
max O_2 flow (L/min)	7.4 ± 3.9	8.7 ± 6.3	0.69
RHI (%)	1.8 ± 0.4	1.6 ± 0.3	0.31
Heart rate (/min)	80.6 ± 11.6	83.1 ± 14.6	0.75
Diastolic BP (mmHg)	84.0 ± 12.5	66.6 ± 6.8	0.02
Systolic BP (mmHg)	132.4 ± 24.6	105.8 ± 19.8	0.09

Values shown are mean ± SD.
F: female; M: male; BMI: body mass index; BP: blood pressure; ICU: intensive care unit; RHI: reactive hyperaemia index; CT: computed tomography; SD: standard deviation.

Table 3
Comparisons of second visit assessments between COVID-19 patients who did not improve (n = 5) and patients who improved (n = 7) their RHI between the first and second visit.

	No improvement in RHI (n = 5)	Improved RHI (n = 7)	p value
Weight (kg)	84.8 ± 15.6	84.7 ± 16.1	0.99
Voorrips score	8.3 ± 10.2	7.2 ± 4.5	0.86
6-MWD (metres)	564.8 ± 68.8	514.1 ± 91.3	0.32
6-MWD (%)	96.8 ± 4.9	95.9 ± 8.3	0.82
Diastolic BP (mmHg)	78.2 ± 11.9	81.3 ± 7.5	0.59
Systolic BP (mmHg)	120.6 ± 9.0	131.6 ± 11.6	0.11
RHI (%)	1.90 ± 0.40	2.95 ± 0.94	0.04
RHI improvement (%)	5.4 ± 5.5	83.2 ± 49.1	0.03
Heart rate (/min)	69.6 ± 7.6	74.3 ± 11.2	0.44
mMRC scale	2.50 ± 1.00	1.80 ± 0.45	0.20
FEV_1 (%pred.)	97.8 ± 8.0	96.9 ± 15.4	0.90
FVC (%pred.)	98.2 ± 4.5	98.5 ± 6.7	0.97
TLC (% pred.)	90.2 ± 8.8	95.3 ± 14.8	0.51
TLCO (% pred.)	70.4 ± 11.1	69.7 ± 17.7	0.94
KCO (% pred.)	91.8 ± 8.2	83.4 ± 9.4	0.14

All values shown are mean ± SD.
6-MWD: 6-min walking distance; BP: blood pressure; RHI: reactive hyperaemia index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; mMRC scale: modified Medical Research Council dyspnea scale; TLC: total lung capacity; TLCO: transfer factor for carbon monoxide; KCO: carbon monoxide transfer coefficient; SD: standard deviation.

Currently, the mechanisms of recovery of endothelial function are warranted to understand the post-COVID complications. Indeed, it is now admitted that the recovery of endothelial cell injury constitutes a key-issue in the long-term complications. A recent study demonstrated that the lack of decrease of plasma Ang2 10 days after COVID-19 infection was associated with a lack of recovery of pulmonary lesions [41]. The recovery of endothelial dysfunction could be related to the mobilization of endothelial progenitor cells because endothelial colony-forming cells (ECFC) increased three months after COVID-19 infection [42]. Because these ECFCs are vasculogenic in vivo, the endothelial dysfunction reported in our COVID-19 patients could be rescued by a pool of stem and progenitor cells. This hypothesis should be investigated in further studies. Besides reported improvements, few COVID-19 patients showed persistent endothelial dysfunction more than 12 weeks after their infection. Indeed, 2/12 (17%) patients had an RHI of <1.67. Reduced RHI <1.67 has also been reported in 10/30 post-COVID syndrome patients [43]. This persistence of endotheliopathy in a subset of COVID-19 patients who do recover endothelial dysfunction could affect brain functions, including mood [7], which was impaired in 40% of our COVID-19 patients. Physical inactivity (all patients had a Voorrips score of <9.4) after hospital discharge could explain this incomplete recovery. Indeed, physical activity improves endothelial function [44].

Our study has several limitations. It is based on a small sample size and a few patients were lost to follow-up. The RHI threshold, which allows classification of patients with improvement in their endothelial function, is based on the range of variation between days identified in a study and requires further evaluation in prospective studies. However, our study has the merit of prospectively assessing consecutive patients in a systematic manner, with a re-assessment that has allowed paired statistical tests, in contrast to other COVID-19 studies. In addition, we included age-matched healthy control subjects. However, our patients were more likely to be male with a history of tobacco smoking and hypertension and an increased BMI, in line with the epidemiology of COVID-19 [45].

5. Conclusion

All in all, post-occlusive assessment of PAT in patients with severe to critical COVID-19 infection revealed impaired RHI values versus healthy controls, indicating an impairment of endothelium-dependent reactivity of the systemic arteries. Nevertheless, recovery of endothelium-dependent function was observed more than four months after infection. However, a small subset of convalescent COVID-19 patients with the most severe acute inflammation at admission did not improve their RHI. These results underline the involvement of the endothelium in patients who recovered from SARS-CoV-2 infection, but further studies are needed to better understand the potential role of confounding factors including inflammation, physical activity and underlying cardiovascular diseases and their impact on endothelial dysfunction and injury in convalescent COVID-19 patients.

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Declaration of Competing Interest

None.

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