Early microvascular modifications in patients previously hospitalized for COVID-19: comparison with healthy individuals

P. Malerba[1], C. Agabiti Rosei[1], M. Nardin[1], A. Gaggero[1], G. Chiarini[1], C. Rossini[1], F. Fama'[1], V. Brami[1], M.A. Coschignano[1], M.L. Muiesan[1], D. Rizzoni[2], C. De Ciuceis[1]

[1]University of Brescia, Internal Medicine, Department of Clinical and Experimental Sciences, Brescia, Italy; [2]University of Brescia, Division of Medicine, Montichiari Hospital, Brescia, Italy

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Background: SARS-CoV2 infection has been associated to a wide range of clinical scenarios, named COVID-19, ranging from acute respiratory distress syndrome to blood coagulation abnormalities and vascular manifestations related to hyper-inflammation. Recent focus has been addressed to study of microvascular alterations which may explain COVID-19 pathophysiology. Alterations in microvascular structure, identified as increased wall to lumen ratio (WLR) of retinal arterioles, have been extensively described in patients with cardiovascular diseases, such as hypertension or diabetes mellitus. Both inflammation and immune system dysregulation seem to play a role in the pathogenesis of these morphological changes.

Purpose: Aim of this study was to evaluate through Adaptive Optics microvascular differences of retinal arterioles between patients experienced COVID-19 and controls.

Methods: Patients were hospitalized between 28th February and 15th April at a Internal Medicine ward in a tertiary care hospital. All patients tested positive for a SARS-CoV-2 nasopharyngeal swab at admission and showed signs of pneumonia and respiratory insufficiency. Adaptive Optics, which allows a non-invasive evaluation of retinal arteriole structure, and blood chemistry exams were performed as part of follow up visits between 2 to 3 months after hospitalization. Baseline characteristics were collected through medical records. COVID-19 patients were compared to age- and sex-matched healthy subjects referred to our center between 2018 and 2019.

Results: A total of 80 patients were included in this study (of which 40 were COVID-19 patients). Apart from smoking habit, other baseline characteristics (sex, age, cardiovascular risk factors and main comorbidities) did not differ between the two groups. At follow up visit COVID-19 patients showed lower values for leukocytes (6.2 vs. 7.5x10^3/µL, p=0.015) and lymphocytes (1.9 vs. 2.8x10^3/µL, p=0.002). Creatinine values were higher in patients who suffered from COVID-19 (1.0 vs 0.8 mg/dl, p=0.004 – Figure 1, panel A). Adaptive Optics showed no differences in terms of internal lumen, wall thickness and WLR of retinal arterioles. However, the wall cross-sectional area (WCSA) was found to be higher in COVID-19 patients (p=0.039 – Figure 1, panel B). Hypertension significantly affected both WCSA and WLR between COVID-19 and healthy individuals, while diabetes only impacted on WLR (Figure 2).

Conclusion: Previous studies described the presence of leukopenia and lymphopenia during the acute phase of SARS-CoV2 infection. Our study demonstrates that these alterations persist several weeks after symptoms onset. Adaptive Optics showed microvascular alterations occurring in these patients: in particular, higher wall cross-sectional area of retinal arterioles were observed in patients after COVID-19 hospitalization, reflecting the complex pathogenic mechanisms which may explain the wide range of symptoms and clinical severity.

A

	COVID-19 patients (n=40)	Healthy individuals (n=40)	p-value
Age (years)	59.8 (±10.6)	63.4 (±6.3)	0.077
Male sex (%)	60	42.5	0.179
Hypertension (%)	37.5	37.5	1.000
Other CV disease (%)	25	17.5	0.586
Active/former smoking (%)	18.8	47.5	**0.022**
Obesity (%)	19.4	17.5	1.000
Diabetes (%)	12.5	10.0	1.000
Ace-inhibitors (%)	15.4	15.4	1.000
Angiontensin receptor blockers (%)	12.8	10.0	0.737
Statines (%)	27.5	25.0	1.000
Systolic blood pressure (mmHg)	131 (±13)	126 (±10)	0.115
Diastolic blood pressure (mmHg)	81 (±7)	79 (±6)	0.255
WBC (x10^3/µl)	6.2 (±1.5)	7.5 (±2.7)	**0.015**
Hemoglobin (g/dl)	13.6 (±1.2)	13.7 (±2.5)	0.787
Lymphocytes (x10^3/µl)	1.9 (±0.7)	2.8 (±1.2)	**0.002**
Creatinine (mg/dl)	1.0 (±0.2)	0.8 (±0.2)	**0.004**

B

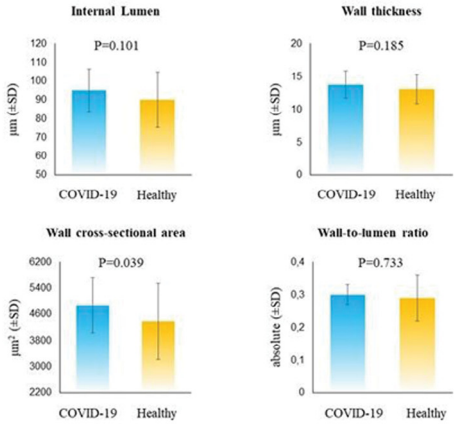

Figure 1

WCSA (µm²)	COVID-19	Healthy	p-value	p-interaction
Age				
<65 y	4829	4409	0.204	0.720
≥65 y	4951	4356	0.107	
Sex				
Female	4769	4430	0.293	0.529
Male	4940	4295	0.090	
Hypertension				
Yes	5189	4056	0.006	0.034
No	4681	4572	0.705	
Diabetes				
Yes	5093	3704	0.079	0.207
No	4840	4443	0.117	
Obesity				
Yes	4378	4174	0.745	0.581
No	4994	4423	0.048	

Wall-to-lumen ratio	COVID-19	Healthy	p-value	p-interaction
Age				
<65 y	0.29	0.30	0.545	0.141
≥65 y	0.32	0.29	0.098	
Sex				
Female	0.28	0.29	0.660	0.603
Male	0.31	0.31	0.762	
Hypertension				
Yes	0.31	0.27	<0.001	0.003
No	0.29	0.32	0.163	
Diabetes				
Yes	0.31	0.24	0.009	0.047
No	0.30	0.30	0.814	
Obesity				
Yes	0.29	0.27	0.374	0.488
No	0.30	0.30	0.797	

Figure 2