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Original Article

Evaluation of early and late COVID-19-induced vascular changes with OCTA

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Objective: To evaluate vascular changes in the early period after coronavirus disease 2019 (COVID-19) infection and at 6-month follow-up.

Methods: This study included 50 eyes of 25 patients who had been hospitalized for polymerase chain reaction–positive COVID-19 infection and 50 eyes of 25 healthy individuals. All subjects underwent optical coherence tomography angiography using a 6 × 6 macular protocol in the early period after hospital discharge and 6 months later. Foveal vessel density (VD) and parafoveal VD values were measured from 4 quadrants (superior, inferior, nasal, and temporal) of the superficial capillary plexus (SCP) and the deep capillary plexus (DCP). The choriocapillaris (CC) flow area and the foveal avascular zone area also were measured. The OCTA measurements of the patient group were compared both between time points and with the control group at each time point.

Results: COVID-19 patients showed lower VD values than control subjects in all parafoveal quadrants of both the SCP (superior, $p = 0.01$; inferior, $p = 0.048$; nasal, $p = 0.003$; temporal, $p = 0.048$) and the DCP (superior, $p = 0.001$; inferior, $p = 0.011$; nasal, $p = 0.012$; temporal, $p = 0.018$) at the initial checkup and in all parafoveal quadrants of the SCP (superior, $p = 0.0001$; inferior, $p = 0.007$; nasal, $p = 0.001$; temporal, $p = 0.017$) and in 2 of the parafoveal quadrants of the DCP (superior, $p = 0.003$; inferior, $p = 0.016$) at 6-month follow-up. CC flow area values were significantly lower at the 6-month follow-up than at the initial examination ($p = 0.044$).

Conclusion: It is important to perform appropriate follow-up for COVID-19 patients because retinal vascular flow changes may persist in the long term.

Objectif: Évaluer l'état vasculaire peu de temps après avoir eu la COVID-19 (maladie à coronavirus 2019) et lors du suivi à 6 mois.

Méthodes: Cette étude a réuni 50 yeux de 25 patients qui avaient été hospitalisés en raison de la COVID-19 – diagnostiquée par un test reposant sur une réaction en chaîne de la polymérase – et 50 yeux de 25 sujets sains. On a obtenu des images réalisées par angiographie-tomographie par cohérence optique (OCTA,) conformément à un protocole maculaire 6 × 6 peu de temps après le départ de l'hôpital de même que 6 mois plus tard. La densité vasculaire (DV) de la zone fovéale et de la zone parafovéale a été mesurée dans les 4 quadrants (supérieur, inférieur, nasal et temporal) du plexus capillaire superficiel (PCS) et du plexus capillaire profond (PCP). On a également calculé l'aire du débit de la choriocapillaire de même que l'aire de la zone fovéale avasculaire. On a comparé entre elles les images de l'OCTA obtenues chez les patients lors des 2 intervalles temporels, et ces images en outre ont été comparées avec celles du groupe témoin à chacun des intervalles temporels.

Résultats: Les patients du groupe COVID-19 avaient une DV inférieure à celle des sujets témoins dans tous les quadrants de la zone parafovéale du PCS (supérieur : p = 0,01; inférieur : p = 0,048; nasal : p = 0,003 et temporal : p = 0,048) et du PCP (supérieur : p = 0,001; inférieur : p = 0,011; nasal : p = 0,012 et temporal : p = 0,018) lors de l'examen initial de même que dans tous les quadrants de la zone parafovéale du PCS (supérieur : p = 0,0001; inférieur : p = 0,007; nasal : p = 0,001 et temporal : p = 0,017) et dans 2 quadrants de la zone parafovéale du PCP (supérieur : p = 0,003 et inférieur : p = 0,016) lors du suivi à 6 mois. L'aire du débit de la choriocapillaire était significativement inférieure lors du suivi à 6 mois que lors de l'examen initial (p = 0,044).

Conclusion: Il est important de réaliser un suivi approprié des patients qui ont été infectés par la COVID-19 en raison du risque de persistance à long terme des altérations du débit vasculaire rétinien.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19), was identified in January 2020 following research conducted to investigate a group of patients with respiratory symptoms such as fever, cough, and shortness of breath in the Wuhan Province of China. COVID-19 shows a pathology ranging from minimal symptoms to acute respiratory distress syndrome and multiorgan damage.[1]

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Complement activation and the intense inflammatory response caused by SARS-CoV-2 can lead to microvascular damage and coagulopathy, which, in turn, can lead to multisystemic organ damage.[2] SARS-CoV-2 can directly impair endothelial cell function by binding to angiotensin-converting enzyme 2 (ACE2). This virus can cause endothelial cell damage from the inflammatory response it triggers, leading to widespread vascular damage.[3]

Because of its multisystemic nature, COVID-19 can also affect ocular tissues. The presence of the virus in conjunctival swabs on the ocular surface has been demonstrated by polymerase chain reaction (PCR).[4,5] Because of its dense microvascular circulation, the retina can be affected by microvasculopathy caused by COVID-19. Abrishami et al.[6] reported that COVID-19 can cause retinal ischemia.

Optical coherence tomography angiography (OCTA) is a modern, noninvasive, repeatable technology that uses an algorithm to measure blood flow velocity using serial measurements of vascular flow taken at the same point. This study aimed to compare short- and long-term OCTA changes in patients who were hospitalized with PCR-positive COVID-19 infection but who did not have a history of intubation or intensive care hospitalization with a healthy control group.

Methods

This study was carried out with the approval of the Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee and in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

The study included patients who were hospitalized between May and June 2020 because of PCR-positive COVID-19 infection who had no history of intubation or intensive care hospitalization and who had been discharged after becoming PCR negative. Thus, all patients were PCR-positive at admission and PCR-negative at discharge. OCTA imaging was performed for each subject shortly after discharge and at a 6-month follow-up. A control group with similar age and sex demographics was selected from healthy subjects who presented at our ophthalmology clinic for routine ophthalmologic examination.

The best corrected visual acuity of each subject was measured with a Snellen chart. Intraocular pressure and pachymetric values also were recorded. Slit-lamp anterior segment and fundus examinations were performed. Foveal vascular flow changes were evaluated using the OCTA 6 × 6 macular protocol.

All patients volunteered to participate in this study. The majority of the study group consisted of hospital personnel. No patients showed a second COVID-19 infection or a new systemic disease after discharge. Two patients were lost to follow-up and thus were excluded from the study.

Patients were excluded if they presented with a history of any ocular or systemic disease that could affect retinal circulation (e.g., diabetes, hypertension, or rheumatic diseases) or if they had an intraocular pressure greater than 21 mm Hg, an axial length less than 20 mm or greater than 24 mm, or a substantial refractive error (spherical above +3 D or −3 D; astigmatism above 1.5 D that may affect the OCTA results). In addition, patients who were receiving systemic treatment with agents such as hydroxychloroquine or steroids that might have ocular effects were excluded.

OCTA assessment

OCTA was used to measure deep capillary plexus (DCP) and superficial capillary plexus (SCP) vessel density (VD) in the foveal area as well as DCP and SCP VD within 4 quadrants (superior, inferior, nasal, and temporal) of the parafoveal area. OCTA also was used to evaluate choriocapillaris (CC) flow area and foveal avascular zone (FAZ) area. Data were compared both between the initial measurements and the 6-month follow-up and between the patient group and the control group.

A single technician performed all scans using the same device at the same time of day (between 10 A.M. and 2 P.M.) following pupil dilation with tropicamide. For infection-control purposes, assessments of normal subjects were performed after all COVID-19 patients had completed their participation in the study. OCTA images were obtained using the AngioVue Imaging System version 2017.1 (Optovue Inc, Fremont, Calif.). A previously described algorithm was used for OCTA that included obtaining OCT three-dimensional macular images and activating the eye-tracking system. The device used in this study had two scanning area options (6 × 6 mm and 3 × 3 mm). Because we believe that 6 × 6 mm scans may be better than 3 × 3 mm scans in the evaluation of vascular changes, and considering that a wider field of view would increase the sensitivity of additional areas of capillary nonperfusion, we used 6 × 6 mm scans in our study.

The automated quality index (scored between 0 and 10) provided by the AngioVue Imaging System was used to assess the quality of the scans, and the scans with a quality index of 7 or greater were included. Low-quality scans (signal strength index < 7) were excluded, and patients were reimaged until satisfactory image quality (≥ 7) was obtained.

For both the SCP and DCP, VD values were calculated for the four quadrants of the parafoveal zone and for the foveal zone. In addition, CC flow area and FAZ area were calculated.

Previously defined retinal and choroidal layers automatically identified by the software algorithm were used.[7] The upper and lower boundaries of the SCP were 3 μm below the internal limiting membrane and 15 μm below the inner plexiform layer, respectively. The DCP was defined as the region between 15 and 70 μm below the inner plexiform layer. The upper and lower boundaries of the CC layer were considered to be 30 and 60 μm below the retinal pigment epithelium, respectively.

Table 1—Mean age and sex distribution for both groups

Parameter	Control Group (n = 25)	COVID-19 Group (n = 25)	*p*-Value
Age, y	38.56 ± 11.58	39.88 ± 10.93	0.674*
Sex			
Male	13 (48.15%)	12 (48.00%)	0.991†
Female	14 (51.85%)	13 (52.00%)	

*Independent *t* test.
†χ^2 test.

Foveal zone VD was defined as the percent density of vessels in a 1-mm-diameter circle. The parafoveal zone VD was defined as the percent density of vessels in the area within a 3-mm-diameter circle excluding the foveal zone. To calculate VD, a binary image of the blood vessels was extracted from the greyscale OCTA image using AngioVue Analytics software (Optovue Inc). Next, the percentage of pixels with a flow signal greater than a specific threshold was calculated for the relevant region and layer. Parafoveal zones were automatically divided into quadrants (temporal, nasal, inferior, and superior).

The FAZ area was defined as the area without vessels within the fovea and automatically calculated by the OCTA software. CC flow area was defined as the area in the 6 × 6 mm macular angiogram within the CC layer with evidence of flow, which was also calculated by the OCTA software.

Statistical analysis

All statistical analyses were performed using Number Cruncher Statistical System 2007 Statistical Software (Kaysville, Utah). In addition to calculating descriptive statistical methods (mean and standard deviation), Shapiro–Wilk normality tests were used to examine the distribution of variables, independent *t* tests were used to compare normally distributed variables in binary groups, paired *t* tests were used to compare the first examination with the 6-month follow-up, and χ^2 tests were used to compare qualitative data. Results were considered significant at a threshold of $p < 0.05$.

Results

This study included 50 eyes of 25 patients hospitalized and discharged because of PCR-positive COVID-19 infection and 50 eyes of 25 healthy subjects as a control group. There were no statistically significant differences in either mean age or gender distributions between the patient group and the control group. The demographic data of the study participants are shown in Table 1.

As detailed in the *Methods* section, all scans were obtained with a signal strength index of 7 or higher. There were no statistically significant differences in the signal strength index values between the two groups (Table 2).

At the first examination, the OCTA data of the COVID-19 group showed lower VD values than those of the control group in all 4 parafoveal quadrants of the SCP (superior, $p = 0.01$; inferior, $p = 0.048$; nasal, $p = 0.003$; temporal, $p = 0.048$) and in all 4 parafoveal quadrants of the DCP (superior, $p = 0.001$; inferior, $p = 0.011$; nasal, $p = 0.012$; temporal, $p = 0.018$). At the 6-month follow-up appointment, VD values were found to be lower in the patient group than in the control group in all 4 parafoveal quadrants of the SCP (superior, $p = 0.0001$; inferior, $p = 0.007$; nasal, $p = 0.001$; temporal, $p = 0.017$) and in 2 of the parafoveal quadrants of the DCP (superior, $p = 0.003$; inferior, $p = 0.016$). No significant differences were found between the patient group and the control group in terms of foveal SCP VD values, foveal DCP VD values, CC flow area, or FAZ area at either the initial check-up or the 6-month follow-up (Table 3).

The initial examination OCTA data and the 6-month follow-up data also were compared within the study group. It was found that the 6-month follow-up CC flow area values were significantly lower than the initial examination CC flow area values ($p = 0.044$). No other significant differences were observed.

Discussion

This study compared OCTA data between healthy control subjects and patients who had been hospitalized with PCR-positive COVID-19 infection and who did not have a history of intubation or hospitalization in intensive care. We report that compared with the control group, the patient group showed significantly lower VD values in all parafoveal quadrants of both the SCP and the DCP in the early period as well as in all parafoveal quadrants of the SCP and 2 (superior, inferior) of the parafoveal quadrants of the DCP at 6-month follow-up. When the early period and the 6-month follow-up OCTA data were compared within the patient group, we found that the CC flow area measurements had significantly decreased at the 6-month follow-up.

Table 2—Signal strength index values of groups

Time of Study	Number	Control Group (n = 25)	COVID-19 Group (n = 25)	*p*-Value*
Early period	7/10	11 (20.37%)	8 (16.00%)	0.804
	8/10	23 (42.59%)	21 (42.00%)	
	9/10	20 (37.04%)	21 (42.00%)	
Six-month follow-up	7/10	11 (20.37%)	13 (26.00%)	0.792
	8/10	23 (42.59%)	20 (40.00%)	
	9/10	20 (37.04%)	17 (34.00%)	
	p-Value†	—	0.067	

*χ^2 test.
†McNemar's test.

Table 3—Foveal and parafoveal VD percentages of the superficial and deep capillary plexuses, FAZ measurements, and CC flow area values in the four quadrants in the early period and at 6 months in COVID-19 patients and healthy control subjects

Factor	Time of Study	Control Group (n = 25)	COVID-19 Group (n = 25)	p Value*
Parafoveal superficial superior VD (%)	Early period	51.82 ± 3.37	49.63 ± 4.98	**0.01**
	At 6 months		49.09 ± 4.54	**0.0001**
	p Value†		0.365	
Parafoveal superficial inferior VD (%)	Early period	51.52 ± 4.00	49.89 ± 4.25	**0.048**
	At 6 months		48.92 ± 5.51	**0.007**
	p Value†		0.099	
Parafoveal superficial nasal VD (%)	Early period	49.99 ± 4.01	47.47 ± 4.33	**0.003**
	At 6 months		47.2 ± 4.8	**0.001**
	p Value†		0.650	
Parafoveal superficial temporal VD (%)	Early period	48.80 ± 4.18	47.16 ± 4.01	**0.048**
	At 6 months		46.92 ± 4.55	**0.017**
	p Value†		0.631	
Parafoveal deep superior VD (%)	Early period	55.16 ± 3.70	52.31 ± 4.52	**0.001**
	At 6 months		52.83 ± 4.45	**0.003**
	p Value†		0.352	
Parafoveal deep inferior VD (%)	Early period	54.44 ± 3.73	52.36 ± 4.44	**0.011**
	At 6 months		52.42 ± 4.98	**0.016**
	p Value†		0.911	
Parafoveal deep nasal VD (%)	Early period	55.08 ± 3.89	53.07 ± 4.03	**0.012**
	At 6 months		54.05 ± 3.53	0.148
	p Value†		0.052	
Parafoveal deep temporal VD (%)	Early period	54.78 ± 3.73	52.99 ± 3.72	**0.018**
	At 6 months		53.56 ± 4.3	0.068
	p Value†		0.336	
Superficial foveal VD (%)	Early period	17.64 ± 5.51	17.43 ± 7.36	0.870
	At 6 months		17.03 ± 6.56	0.604
	p Value†		0.199	
Deep foveal VD (%)	Early period	33.91 ± 7.03	32.09 ± 8.41	0.230
	At 6 months		32.55 ± 8.07	0.359
	p Value†		0.440	
CC flow area (mm^2)	Early period	2.08 ± 0.11	2.15 ± 0.23	0.059
	At 6 months		2.09 ± 0.13	0.872
	p Value†		**0.044**	
FAZ (mm^2)	Early period	0.29 ± 0.11	0.31 ± 0.13	0.283
	At 6 months		0.30 ± 0.12	0.514
	p Value†		0.442	

Bolded *p*-values below 0.05 were considered statistically significant.
VD, vessel density; FAZ, foveal avascular zone; CC, choriocapillaris.
*Independent *t* test.
†Paired *t* test.

Coronaviruses consist of 4 structural proteins: spike (S) protein, membrane (M) protein, envelope (E) protein, and nucleocapsid (N) protein. Previous studies have reported that the S protein of SARS-CoV-2 is the functional receptor for ACE2.[8] Although ACE2 is known to be expressed at high rates in lung, heart, ileum, kidney, and bladder epithelial cells, this receptor is expressed at various levels in almost every organ in the body.[9,10] In addition, ACE2 receptors are present in all endothelial cells, especially in the heart, lungs, kidneys, and gastrointestinal system.[11]

SARS-CoV-2 infection of endothelial cells can lead to many tissue changes, including ischemia, edema, and hypercoagulability. In addition, immune mediators such as tumour necrosis factor α, interleukin 1, and interleukin 6 can greatly increase because of the intense inflammatory response caused by COVID-19, which may lead to coagulopathy or thrombosis owing to an increase in leukocyte adhesion to endothelial cells. This increase in inflammatory mediators can lead to acute respiratory distress syndrome, disseminated intravascular coagulation, or hypercoagulation.[12]

The retina has a dense vascular structure and therefore is vulnerable to changes from COVID-19 owing to the diffuse microangiopathy caused by this disease. Abrishami et al.[6] conducted an OCTA study in patients with recent COVID-19 infection and reported that patient parafoveal VD values were decreased in the DCP and the SCP. In that study, 3 × 3 mm scans were used. In contrast, larger-area scans (6 × 6 mm) were used in our study, and parallel findings were obtained. Another study reported that perfusion density was low in the radial peripapillary capillary plexus following COVID-19 infection.[13] Further, retinal hemorrhages, cotton wool spots, dilated veins, and increased venous tortuosity have each been detected by fundus examination of individuals infected with COVID-19, and patients were reported to show increased diameters of both arteries and veins compared with a control group.[14] Acute macular neuroretinopathy and paracentral acute middle maculopathy inducing sudden vision loss, negative scotomas, and dyschromatopsia are among the complications of COVID-19 infection reported in the literature.[15] In agreement with previous studies, our study reports a decrease in VD values measured with OCTA in all parafoveal quadrants of the SCP and DCP in the early period after COVID-19 infection.

While trying to elucidate the pathogenesis of inflammation and ischemia-based microvascular changes caused by COVID-19, a new term, *long COVID*, has recently come

into use to refer to the symptoms of COVID-19 that are prolonged for longer than expected. For example, 87% of people hospitalized for COVID-19 infection in Italy who were evaluated an average of 60 days after discharge still continued to experience COVID-19 symptoms.[16] Additionally, in a study of 384 patients who were followed up for an average of 54 days after acute COVID-19 infection, continuous shortness of breath was reported in 53%, cough in 34%, fatigue in 69%, and depression in 14.6%. In the same study, high D-dimer and C-reactive protein values were found at follow-up, especially in those who were discharged with high D-dimer and C-reactive protein values.[17] Puntmann et al.[18] reported ongoing myocardial inflammation on cardiac magnetic resonance imaging after SARS-Cov-2 infection, emphasizing the necessity of late follow-up. In agreement with these previous studies, our study reports decreased VD values for all parafoveal quadrants of the SCP and for 2 parafoveal quadrants (superior, inferior) of the DCP at 6-month follow-up in a patient group compared with a group of healthy control subjects. When patient data from the early period after infection and the 6-month follow-up were compared, a decrease in CC flow area values was found.

As discussed earlier, COVID-19 infection can exert long-term systemic effects in the lung and cardiac tissues. In particular, long-term OCTA examinations of tissues with high blood supply, such as the retina and choroid, show that persistent vascular flow changes can continue in the long term because of the direct effects of the infection or the indirect effects of ongoing systemic changes. These findings are also seen in the acute period following COVID-19 infection.

Vasodilation/vasoconstriction response varies depending on oxygen−carbon dioxide imbalance. This is especially relevant for choroidal tissue because it has the highest blood supply per unit in the body. Kitazono et al.[19] reported that high carbon dioxide levels cause vascular relaxation and thus vasodilation. Another study performed with a laser Doppler flowmeter in healthy individuals showed that choroidal blood flow increases in response to hypoxia[20] In our study, the decrease we found in CC flow area values when comparing the early period after COVID-19 infection and 6-month follow-up may have been owing to regression of the hypoxic environment in the CC leading to reactive vasoconstriction. This change is perhaps an early indicator of local vascular improvement following infection with SARS-CoV-2.

Our study has several limitations, the main of which is the limited number of cases. In the future, studies with a larger number of cases are needed. Although OCTA is a contemporary technology with continuously increasing usage, there is still a need for better algorithms to correct artifacts that may occur during imaging. However, performing follow-up imaging of patients provides a better understanding of possible long-term changes. Despite these limitations, to our knowledge, this is the first study in the literature to investigate OCTA changes in the early period and 6 months later in patients who were hospitalized with PCR-positive COVID-19 infection.

In conclusion, this study performed OCTA examinations in the early period after COVID-19 hospitalization and 6 months later and investigated changes in these results over time as well as differences between patient results and those of healthy control subjects. We detected a decrease in VD in all parafoveal quadrants of the SCP and the DCP in the early period as well as in the parafoveal region of the SCP for all quadrants and the DCP for the superior and inferior quadrants at the 6-month follow-up. In addition, when comparing changes over time between the early period and the 6-month follow-up, we found a decrease in CC flow area values. Multicentred long-term studies with large numbers of cases are needed to clarify the early and long-term retinal and choroidal vascular changes caused by COVID-19.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.

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