

Optic Nerve Head Optical Coherence Tomography Angiography Findings in Patients with Coronavirus Disease 2019

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Abstract

Purpose: To quantify the microvasculature density of the optic nerve head (ONH) using optical coherence tomography angiography (OCTA) analysis in patients recovered from Coronavirus Disease 2019 (COVID-19)

Methods: In a comparative cross-sectional, observational study patients recovered from COVID-19, whom diagnosis of COVID-19 was confirmed by a positive reverse transcription-polymerase chain reaction of a nasopharyngeal sample were included in this study. The OCTA of ONH was performed at least 2 weeks after recovery from systemic COVID-19. Vascular density (VD) of the all vessels (AV) and small vessels (SV) inside the disc and radial peripapillary capillary (RPC) network density were measured in COVID-19 recovered patients and compared with similar parameters in an age-matched group of normal controls.

Results: Twenty-five COVID-19 patients and 22 age-matched normal controls were enrolled in the study and one eye per participant was evaluated. Mean whole image SV VD in the COVID-19 group (49.94 ± 2.22) was not statistically significantly different from that in the control group (49.31 ± 1.93 ; p -value= 0.308). An increase in RPC VD was found in all AV and SV VD measured, which became statistically significant in whole peripapillary SV VD, peripapillary inferior nasal SV VD, peripapillary inferior temporal SV VD, peripapillary superior nasal SV VD and grid-based AV VD inferior sector ($p < 0.05$ for all comparisons).

Conclusion: Unremarkable increase was found in ONH microvasculature in patients who had recovered from COVID-19. These patients may be at risk of ONH vascular complications.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new member of the Coronaviridae family of viruses, which can cause serious life-threatening respiratory illness, severe pneumonia,¹ and even multiorgan failure.^{2,3} Various clinical presentations and fatal consequences of the associated disease, Coronavirus Disease 2019 (COVID-19), have been reported, but scarce reports regarding ocular manifestations are available.^{4,5}

Angiotensin-converting enzyme (ACE)-2 is considered as the main receptor for SARS-CoV-2 infection.⁶ ACE2 as a member of the renin-angiotensin-aldosterone system (RAAS) is present in different cell types including type II alveolar cells in the lung, arterial and venous endothelial cells, enterocytes of the small intestine, and smooth muscle cells of arterial vasculature of most organs.⁷ Its homologous enzyme is ACE, which is the main effector in the RAAS and ACE2 counterbalances and regulates its activity by reducing the amount of angiotensin-II and increasing Ang (1-7).⁸ ACE and ACE2 have been presented in the choroid and different cell types of the retina including retinal vascular endothelial cell, photoreceptor cells, Müller cells, and ganglion cells.⁹ Moreover, their expression in neurons and glial cells in the CNS

have been reported.¹⁰ Hence, it seems reasonable to expect ocular, and specifically optic nerve head (ONH) and CNS manifestations of the SARS-CoV-2 infection.

The majority of reports on the ocular involvement in COVID-19 describe ocular surface manifestations including conjunctival congestion, chemosis, and conjunctivitis.^{10,11} Reports of the retinal findings are numerable. Marinho and colleagues described various retinal manifestations of COVID-19 like cotton wool spots and hemorrhages,¹² but these findings were called into question.¹³

Optical coherence tomography angiography (OCTA) is capable of depth-resolved imaging of blood flow in different retinal layers and differentiate various vascular sizes.¹² In this study, we used OCTA to evaluate the ONH vasculature in patients recovered from COVID-19 and compare it with a normal group.

Methods

Study participants

A cross-sectional study was conducted at the Imam Reza General Hospital, Mashhad, Iran. Nurses and physicians working at Mashhad University of Medical Sciences (MUMS) with a definite diagnosis of COVID-19, confirmed by a positive test result of a nasopharyngeal swab sample real-time, reverse transcription-polymerase chain reaction, who recovered from the systemic symptoms at least 2 weeks' prior the enrolment, were included.

Detailed ocular and systemic histories were obtained from each participant and those with a history of auto-immune disease, migraine, diabetes mellitus, current pregnancy and breastfeeding, or any history of intraocular surgery were excluded. Additional exclusion criteria included absolute spherical refractive error greater than 5 diopters and cylindrical refractive error more than 2 diopters, best-corrected visual acuity less than 20/20, and evidence of glaucoma or clinically apparent retinal disease. Those with ocular media opacity, like cataract or corneal haziness, preventing high-quality imaging or reduced OCTA scan quality (i.e. quality scan index less than 7/10) were also excluded from the analysis.

The age-matched control groups were healthy nurses and physicians employed by the MUMS who were imaged on the same OCTA machine at the Imam Reza Hospital in 2019; this group was recruited as part of an ongoing, longitudinal cohort study, PERSIAN Organizational Cohort study in MUMS.

Complete medical systemic history regarding the patients' COVID-19 symptoms, hospitalization and disease course were recorded. Oxygen saturation at the time of examination was measured by a portable pulse oximeter.

Image acquisition and analysis

OCTA scans were performed with the AngioVue (RTVue XR Avanti, Optovue, Fremont, CA, USA; Software version 2018.0.0.14), an OCTA machine with A-scan-rate of 70,000 scans per second. Each B scan line is repeated to evaluate the image decorrelation. Optic disc cubes, AngioDisc 4.5×4.5 mm HD scan (400 lines

× 400 A-scans) protocols, were scanned in the horizontal and vertical orthogonal directions. All measurements were primarily acquired using the automated default segmentation with the preset settings for the radial peripapillary capillary (RPC) network. The 3D Projection Artifact Removal by OCT 3D volume set were utilized.

All images were centered on the optic disc and displayed a scan quality index of at least 7/10. Images with undesirable quality or image artifact were discarded and reacquired. All images in the study, mostly segmentation accuracy, were carefully reviewed by two (MA, RD) to ensure sufficient quality and resolution and any images with artifact significant enough to interfere with vessel density analysis were also excluded. For all subjects, cases or controls, only the data of the eye with better image quality was used for analysis.

To evaluate the RPC layer, a slab between the outer limit of the retinal nerve fiber layer (RNFL) and the internal limiting membrane were used. All the images were checked for segmentation errors and manually adjusted before testing the vessel density. All vessels (AV), including both large and small vessels, and small vessels (SV) VD were evaluated separately in the RPC layer. The whole image, inside disc area, in peripapillary whole, peripapillary superior and inferior hemifields, and eight segments SV RPC VD were reported. For the evaluation of AV VD, including both large vessels and small vessels, the whole image was divided into nine (three by three) grid-based sections, and AV VD in all sections was reported separately. Moreover, the whole image, inside the disc area, in peripapillary whole, peripapillary superior and inferior hemifields AV were reported.

Statistical Analysis

The normal distribution of variables was examined using the Shapiro-Wilk test and normality plots and homogeneity of variances were ascertained by Levene's test. Based on data distribution and type, either the independent-samples t-test, paired t-tests, or Mann-Whitney U test were used for comparisons. Chi-square test and Fisher's exact test were used for categorical variables. The level of statistical significance was set at 0.05. All statistical analyses were performed using the SPSS program for Windows, version 20 (IBM SPSS Statistics, IBM Corporation, Chicago, IL, USA).

Ethical Considerations

The study protocol adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrollment and the ethical aspects of the study were approved by the Regional Committee on Medical Ethics at Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.REC.1399.104).

Results

Twenty-five recovered COVID-19 patients (10 females, 40%) with a mean age of 41.5 ± 10.5 years and 22 healthy normal controls (10 females, 45.4%) with a mean age of 36.7 ± 7.3 years were enrolled in the

study. Age (p -value: 0.086) and gender (p -value: 0.706) were not significantly different between the two groups. ONH parameters like cup-disc ratio and rim area were not different between the groups. (Table 1) None of the patients or controls had other systemic comorbidity except recent COVID-19 in last six months.

All patients were symptom-free for at least 2 weeks. Past medical history was otherwise unremarkable for almost all of the patients and controls. None of the included subjects, COVID-19 cases or controls, endorsed a history of diabetes mellitus. Two COVID-19 patients had a history of grade 1 hypertension which was well controlled with medications or diet. Nine patients (36%) had a history of hospitalization for COVID-19. O_2 saturation was in the normal range (94-99%) in these patients and was not different from non-hospitalized patients (p -value: 0.513). The mean scan quality was 8.28 ± 0.73 in the COVID cases and 8.50 ± 0.67 in the normal controls (p -value: 0.293).

The 4.5×4.5 mm mean whole image SV VD (49.94 ± 2.22) in the COVID-19 group was not statistically different from that in the normal control group (49.31 ± 1.93) (p -value: 0.308) although it seems to be greater in the COVID-19 recovered patients (Table 2). The 4.5×4.5 mm mean whole image AV VD in the COVID-19 cohort (56.44 ± 2.29) was also not statistically significantly different with that in the controls (56.08 ± 1.89) (p -value: 0.566); however, there was a tendency for higher values in the former group (Table 3) (Figure 1).

Of note, whole peripapillary SV VD (53.14 ± 2.31 vs. 51.76 ± 1.92 ; p -value: 0.032), peripapillary inferior nasal SV VD (53.21 ± 4.12 vs. 48.54 ± 2.94 ; p -value: <0.001), peripapillary inferior temporal SV VD (59.78 ± 3.25 vs. 56.93 ± 3.14 ; p -value: 0.004), and grid based AV VD in inferior sector (60.68 ± 2.14 vs. 62.56 ± 3.15 ; p -value: 0.023) were significantly higher in COVID-19 patients, compared with normal controls. In addition, in all other parameters, except inside disc SV VD, COVID-19 patients had higher VD in AV and SV VD, but the differences were not statistically significant. Inside disc SV VD in COVID-19 patients (45.46 ± 6.22) was lower than the inside disc SV VD in the normal control group (49.43 ± 4.96 ; p -value: 0.021).

The difference in the mean AV VD and SV VD was not statistically significant in the hospitalized versus the non-hospitalized COVID-19 patients.

Discussion

In the present study, we used OCTA to determine the vascular density in the ONH and the RPC in a relatively young, mild involved, without other comorbidity and minority hospitalized, cohort of recovered COVID-19 patients and compare it with an age-matched normal control group. Except inside disc SV VD which was less in the COVID-19 patients, in all RPC measured SV and AV VD recovered COVID-19 patients showed higher values, which became statistically significant in whole peripapillary SV VD, peripapillary inferior nasal SV VD, peripapillary inferior temporal SV VD, and grid-based AV VD Inferior sector. In other segments of peripapillary SV VD and grid-based sectors of AV VD, vessel densities tend to be higher in the COVID group but this did not reach statistical significance.

In an autopsy study, Casagrande and associates detected SARS-CoV-2 viral particles in the retina of patients who had deceased due to COVID-19.¹⁴ Presence of ACE2 receptors in CNS and various layers of the retina and choroid have been reported,^{9, 10} hence pathologic changes in the ocular tissues, and especially in ONH and retina, may be expected.

In a recent case series, in seven out of eight patients recovered from COVID-19, RNFL thickness was increased when compared to their available previous examinations¹⁵. The only patient with decreased RNFL thickness had glaucoma. In this case series the mean increase in RNFL thickness was very small (mean: 4.3 μm); however, it indicates probable ONH involvement in COVID-19. Moreover, Guillain-Barré syndrome and Miller-Fisher-like syndrome have also been reported in association with SARS-CoV-2 infection.¹⁶⁻¹⁷ In recent studies SARS-CoV-2 potential for neuroinvasion has been suggested.¹⁸ It seems that in-line with the previous reports of retinitis and optic neuritis induced by coronaviruses in animal models,¹⁹ and the proposed neuroinvasion hypothesis, SARS-CoV-2 can cause neuro-inflammation and neuro-infection in humans, too. Besides the neurologic involvements, as retinal ganglion cells, Müller cells, and blood vessels are potential targets of the virus the ONH and retinal findings in COVID-19 are well anticipated. Vascular changes can be either primary or secondary to alternations in the hemodynamic demands of the inflamed and damaged tissues.

OCTA analysis is an invaluable tool in the evaluation of vascular changes in the retina and ONH for diagnosis, staging, and monitoring in glaucoma.^{20, 21} In addition, in several neurologic conditions, including preclinical Alzheimer's disease, OCTA was found to be helpful.²² In other neurodegenerative diseases and even mild cognitive disorders, OCTA has been proposed as an additional biomarker for the early diagnosis and disease activity monitoring.^{23, 24} In this study, we found that ONH microvasculature was somewhat increased compared to the age-matched controls. In many segments, VD was numerically increased in these comparative analyses, although the differences were not statistically significant.

This study has several limitations. First, OCTA images were acquired during the recovery of the disease and not during the acute phase when the systemic condition was active. Second, longitudinal analysis of the patients was not performed. Third, we had a limited sample size, which can explain the lack of statistical significance in some comparisons. A larger-scale study with OCTA performed during the symptomatic phase of the disease, followed by repeat imaging at fixed intervals, would provide valuable information regarding both the short and long-term effects of COVID-19 on the ONH vascular system.

To the best of our knowledge, it's the first report of ONH OCTA findings in patients with a history of COVID-19. The clinical relevance of our finding is unclear, as the patients were all asymptomatic with 20/20 vision at the time of this analysis. This can indicate the acute inflammatory phase of the ocular involvement and the associated vasodilation. It is noteworthy that the systemic and ocular disease phases can be unparalleled and occur at different times. Nevertheless, our findings in a relatively young group of COVID-19 confirmed patients who had no other comorbidity, and the comparison with an age-matched normal control group, similarly imaged, is novel and may highlight the importance of continued

vigilance for the detection of nervous tissue and ocular complications associated to COVID-19 as the pandemic evolves.

Conclusion

In conclusion, our study demonstrated significant ONH VD alterations in patients with a history of COVID-19 and without other comorbidities, including an increase in all vessels and small vessels VD in the and in some segments of RPC. The potential involvement of the ONH and peripapillary microvasculature by COVID-19 warrants further study.

Abbreviations

COVID-19: Coronavirus Disease 2019

ONH: optic nerve head

OCTA: optical coherence tomography angiography

OCT: optical coherence tomography

SV: small vessels

AV: all vessels

VD: vessel density

RPC: radial peripapillary capillary

RNFL: retinal nerve fiber layer

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ACE: angiotensin-converting enzyme

ACE2: angiotensin-converting enzyme 2

MUMS: Mashhad University of Medical Sciences

FAZ: foveal avascular zone

Declarations

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Compliance with ethics guidelines: The study protocol adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before enrollment and the ethical aspects of the study were approved by the Regional Committee on Medical Ethics at Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.REC.1399.104).

Data availability: The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1: Comparison of optic nerve head parameters and age of COVID-19 patients eyes versus normal eyes.

	Normal Eyes Mean ± SD (Range) 22 Normal Healthy Controls	COVID-19 Patients Eyes Mean ± SD (Range) 25 Recovered Patients	P Value (Compare To Normal)
Age	41.5 ± 10.5 (24-53)	36.7 ± 7.3 (25-61)	0.086
Cup/Disc Area Ratio	0.14 ± 0.09 (0 – 0.33)	0.12 ± 0.10 (0 – 0.35)	0.415
Cup/Disc Vertical Ratio	0.37 ± 0.18 (0 – 0.60)	0.30 ± 0.21 (0 – 0.61)	0.283
Cup/Disc Horizontal Ratio	0.32 ± 0.16 (0 – 0.55)	0.27 ± 0.19 (0 – 0.59)	0.356
Rim Area	1.67 ± 0.27 (1.18 – 2.29)	1.58 ± 0.32 (1.09 – 2.40)	0.313
Disc Area	1.97 ± 0.31 (1.47 – 2.74)	1.81 ± 0.30 (1.22 – 2.40)	0.076
Cup Volume	0.09 ± 0.18 (0 – 0.87)	0.06 ± 0.08 (0 – 0.34)	0.469
Peripapillary RNFL	108 ± 10.77 (101 – 129)	112.04 ± 7.69 (83 – 133)	0.151

RNFL: retinal nerve fiber layer; COVID-19: Coronavirus Disease 2019; SD: Standard Deviation

Table 2: Comparison of small vessels (SV) vessel density (VD) of COVID-19 patients eyes versus normal eyes

	Normal Eyes Mean ± SD (Range)	COVID-19 Patients Eyes Mean ± SD (Range)	P Value
Whole Image- SV VD	49.31 ± 1.93 (44.90 – 53.40)	49.94 ± 2.22 (44.50 – 53.20)	0.308
Inside Disc- SV VD	49.43 ± 4.96 (37.70 – 56.40)	45.46 ± 6.22 (24.80 – 53)	0.021
Whole PeriPapillary- SV VD	51.76 ± 1.92 (47 – 55.20)	53.14 ± 2.31 (46 – 56.70)	0.032
PeriPapillary Superior Hemi- SV VD	52.01 ± 2.16 (46.90 – 55.70)	53.12 ± 2.90 (44.40 – 57.10)	0.148
PeriPapillary Inferior Hemi - SV VD	51.79 ± 3.31 (44.90 – 62)	53.16 ± 2.13 (47.70 – 57.90)	0.095
PeriPapillary Nasal Superior SV VD	49.37 ± 2.96 (42.40 – 53.70)	49.99 ± 3.84 (37.90 – 56.10)	0.547
PeriPapillary Nasal Inferior SV VD	48.20 ± 4.63 (39 – 57.90)	49.52± 4.71 (38 – 64.50)	0.337
PeriPapillary Inferior Nasal SV VD	48.54 ± 2.94 (42.30 – 52.90)	53.21 ± 4.12 (45.40 – 59.50)	<0.001
PeriPapillary Inferior Temporal SV VD	56.93 ± 3.14 (46.60 – 61.50)	59.78 ± 3.25 (53.60 – 65.20)	0.004
PeriPapillary Temporal Inferior SV VD	52.15 ± 3.57 (47.30 – 60.40)	53.69 ± 3 (45.40 – 58.20)	0.632
PeriPapillary Temporal Superior SV VD	55.86 ± 4.02 (44.20 – 61.30)	55.96 ± 4.50 (44.50 – 63.80)	0.889
PeriPapillary Superior Temporal SV VD	55.24 ± 2.76 (50.50 – 60.20)	57.0 ± 3.92 (49.50 – 63.30)	0.087
PeriPapillary Superior Nasal SV VD	49.03 ± 3.39 43.60 – 55.50)	51.14 ± 3.72 (41.20 – 58.70)	0.049

SV: small vessels; VD: vessel density; SD: Standard Deviation; COVID-19: Coronavirus Disease 2019

Table 3: Comparison of all vessels (AV), including both small and large vessels, vessel density (VD) of COVID-19 patients eyes versus normal eyes.

	Normal Eyes Mean \pm SD (Range)	COVID-19 Patients Eyes Mean \pm SD (Range)	P Value
Whole Image – AV VD	56.08 \pm 1.89 (52.50 – 60.20)	56.44 \pm 2.29 (51.40 – 59.10)	0.566
Inside Disc – AV VD	56.05 \pm 4.14 (49.50 – 63.90)	57.25 \pm 5.46 (40.40 – 63.80)	0.057
Whole Peripapillary – AV VD	58.31 \pm 1.65 (55 – 61.80)	59.33 \pm 2.34 (52.90 – 62.60)	0.110
Peripapillary Superior Half - AV VD	58.75 \pm 1.64 (56.10 – 61.50)	59.50 \pm 2.63 (52 – 63.70)	0.257
Peripapillary Inferior Half – AV VD	57.90 \pm 2.08 (53.20 – 62.60)	59.11 \pm 2.30 (53.90 – 63.60)	0.066
Grid Based AV VD Supero temporal	57.63 \pm 4.21 (43.30 – 63.10)	59.14 \pm 3.02 (52.60 – 64)	0.161
Grid Based AV VD Temporal	56.46 \pm 3.08 (46.60 – 62)	57.01 \pm 3.37 (50.40 – 61.50)	0.565
Grid Based AV VD Infero temporal	58.49 \pm 4.47 (42.60 – 64.40)	58.67 \pm 3.43 (49.20 – 64.10)	0.879
Grid Based AV VD Superior	56.85 \pm 2.77 (52.50 – 62.10)	58.68 \pm 3.36 (50.80 – 63.40)	0.051
Grid Based AV VD Central	58.10 \pm 4.56 (50 – 64.60)	60.35 \pm 3.23 (49 – 64.40)	0.061
Grid Based AV VD Inferior	60.68 \pm 2.14 (55.30 – 64.50)	62.56 \pm 3.15 (54.10 – 66.90)	0.023
Grid Based AV VD Supero nasal	51.71 \pm 4.19 (43.90 – 58.20)	52.09 \pm 3.36 (43.60 – 59.90)	0.739
Grid Based AV VD Nasal	52.30 \pm 5.48 (43.80 – 67.90)	52.52 \pm 3.50 (44.60 – 62.40)	0.869
Grid Based AV VD Inferonasal	50.29 \pm 3.91	50.35 \pm 3.84	0.903

AV: all vessels; VD: vessel density; SD: Standard Deviation; COVID-19: Coronavirus Disease 2019

Figures

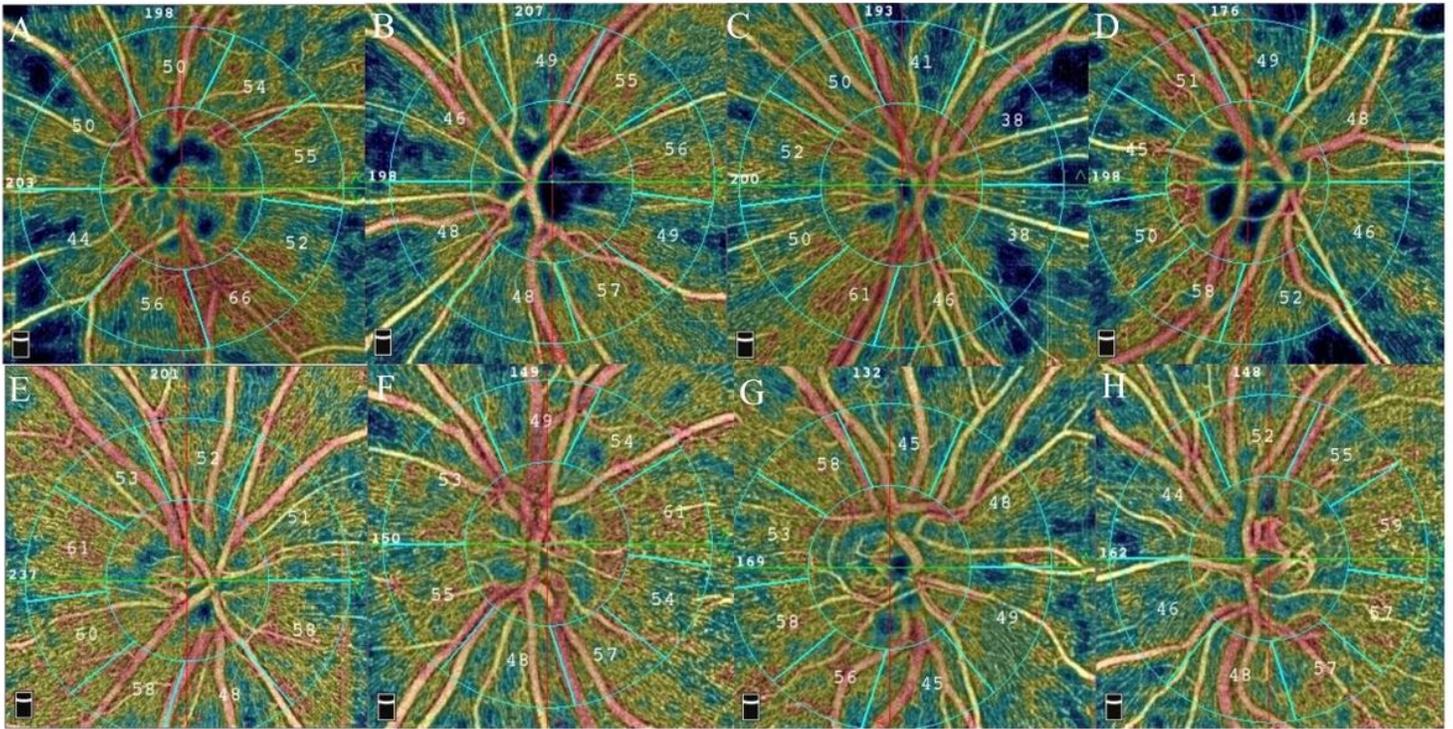


Figure 1

En-face optical coherence tomography angiograms (OCTA) segmented at the level of the radial peripapillary capillary (RPC) network from 4 recovered COVID-19 patients (A-D) versus 4 age matched normal controls (E-H). Note the remarkable flow deficits present in the en-face angiograms from the COVID cases.