Neurology Asia 2025; 30(1) : 165 – 179

Ictal and interictal optical coherence tomography angiography findings in patients with migraine

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Abstract

Background & Objective: Previous studies have suggested that changes in ocular vessels may occur because of vascular mechanisms involved in the pathogenesis of migraine. This study aimed to evaluate the vascular density in the radial peripapillary capillary (RPC) segment by optical coherence tomography angiography (OCTA) in ictal and interictal periods in patients with migraine. *Methods:* In this study, the RPC vessel density was assessed by OCTA in the ictal and interictal periods in the same cohort consisting of 27 patients with migraine with and without aura. The ictal and interictal OCTA results were compared. Statistical analyses were done according to the sociodemographic and clinical data. *Results:* No statistically significant differences were observed in vessel density in either the ictal or interictal periods in patients with migraine with and without aura.
Conclusion: Migraine may not have a direct impact on the RPC vessel density. However, the inconsistent results of OCTA in migraine cases may be due to the differences in the study designs in the literature. The protocols for OCTA use in migraine might help to homogenize study designs and improve data collection.

Keywords: Migraine, optical coherence tomography angiography, ictal and interictal period, vascular density

INTRODUCTION

Migraine is a common headache syndrome. Long-term follow-up studies have shown that patients with migraine are more prone to ischemic cardiovascular and cerebrovascular events than the general population.[1,2]

Visual complaints are common in patients with migraine in both the ictal and interictal periods. Visual field defects and visual perceptual disturbances may be observed during migraine aura, and light sensitivity is a key feature of migraine attacks. Studies have shown that patients with migraine have anatomical and physiological differences in means of changes in the subbasal neural network[3] and differences in retinal rods and related pathways according to individuals without migraine.[4] More than half of the patients complain of blurred vision during the ictal period[5], and this blurring may be due to an imbalance between the sympathetic and parasympathetic nervous systems.[6] The autonomic nervous system is associated with vascular innervation and regulates ocular blood flow.[7] Additionally, since the sensory fibers of the ophthalmic branch of the trigeminal nerve, a component of the trigeminovascular system, innervate the ocular structures, ocular vascular changes may be seen during migraine attacks. However, literature lacks data on whether optical coherence tomography angiography (OCTA) findings differ during the attack and the interictal periods. OCTA is a noninvasive imaging modality with high repeatability and reproducibility.[8,9] OCTA can be used to assess the density of the blood vessels in the eye (the retinal arteries and veins, macular capillaries, optic nerve head vessels, radial peripapillary capillary segment (RPC), choriocapillaris, and choroidal vessels).[10] Radial peripapillary capillaries are a vascular network located around and supplying the optic disc.[10] Vasodilation and/or vasoconstriction

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Date of Submission: 2 March 2024; Date of Acceptance: 6 December 2024
https://doi.org/10.54029/2025amj

may occur in the ocular vessels because of vascular mechanisms involved in the pathogenesis of migraine.[11,12] The real-time visualization of the retinal vascular structures by OCTA may contribute to our knowledge about the impact of migraine attacks on vascular system.

In the present study, we examined whether vascular imaging differed in the ictal and interictal periods in patients with migraine with and without aura by assessing the vascular density measurements of the RPC obtained by OCTA.

METHODS

All headache patients aged 18-55 years who were diagnosed with migraine with or without aura according to the diagnostic criteria of the International Headache Society (ICHD)[13] at the neurology outpatient clinics in two tertiary hospitals (SANKO University Hospital and Dr. Ersin Arslan Training and Research Hospital) were evaluated for eligibility to participate in the study. Patients who had medication overuse headaches, ocular diseases that could affect the ocular vasculature, or had intraocular surgery were excluded.

The subject of the study was explained to all patients who could participate in the study. We explained that the cases who apply to any one of the outpatient clinics in two hospitals in working hours without taking any medication during a migraine attack would have an ophtalmological examination and an OCTA scan following the confirmation of the migraine attack by one of the four neurologists.

For research purposes we prepared a form in advance to record the sociodemographic and clinical data of the enrolled patients separately. On that form we recorded data regarding age, gender, addictions, comorbidities, medications, and clinical features related to migraine attacks (namely, severity, duration, frequency, onset age of the attacks, accompanying symptoms, sensitivity to noise and light, nausea and vomiting, ocular symptoms during attacks, analgesics use, provoking factors, loss of productive time at work/household work and in social life due to headache).

Thirty-one patients who registered during a migraine attack were evaluated quickly by a neurologist who specialized in headache disorder for the features of the migraine attack. The fitting cases were included into the study. Followingly, cases were referred to the SANKO University Ophthalmology Outpatient Clinic for ophthalmological examination and OCTA scans. All patients underwent extensive ophthalmological examination including assessment of best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, central corneal thickness measurement, fundus examination, and OCTA imaging. Eyes with best-corrected visual acuity of 20/20 and a refraction less than 2.0 dioptres sphere and 2.0 dioptres cylinder were included. Eyes with IOP ≥ 21 mm Hg, any retinal or optic disc pathologies, patients with a history of glaucoma, uveitis, ocular trauma, intraocular surgery were excluded. All ophthalmological examinations and OCTA image reviewing were done by experienced ophthalmologists.

Patients whose first OCTA scan was performed during an attack were requested to apply for a second neurological evaluation and OCTA scan in a period when they were free of a migraine attack for at least 7 days. Unfortunately COVID-19 regulations did not ease the follow up visits. So patients were contacted by phone at regular intervals to keep track of their attack-free period and those who did not have any migraine symptoms for at least 7 days were invited for the second OCTA examination during the interictal period. In the following months majority of the cases called us back and reported attack free periods more than 7 days. However for some cases a follow-up contact required multiple phone calls. Twentyseven out of 31 patients presented also during the interictal period. Two individuals could not be contacted by phone, one reported relocation to another city, and one case said he could not come because of transportation problems. Four patients who did not have interictal OCTA scan were excluded from the study. The second OCTA was done strictly in the interictal periods but appointments were adjusted according to the availability of the patient.

Patients who admitted for the second evaluation during the interictal period were re-evaluated face to face by the neurologist who followed them. Once it was confirmed that they were symptom-free for at least 7 days, they were referred to the ophthalmology outpatient clinic for a second OCTA.

OCTA evaluation was performed by experienced ophthalmologists, and the following points were considered for the acquisition technique: Images with a scan quality of ≥8/10 and without segmentation failures or artifacts (e.g. irregular vessel pattern or disc boundary on the enface angiogram, and local weak signal) were only

analyzed. Poor quality images, which were defined as those with a signal strength index (SSI) < 45, were excluded from the analysis. If necessary, repeated measurements were taken until good quality images standards were achieved.

The whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels were measured by the OCTA of 27 patients with migraine with and without aura in the ictal and interictal periods were evaluated and compared separately. In addition, the whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels were compared after stratification of the population according to gender, smoking status, and clinical manifestations of migraine attacks.

Optical coherence tomography angiography measurements

An OCTA device (AngioVue, Optovue, Inc., Fremont, California, USA) was used for vascular imaging. Vessel density within the retinal nerve fiber layer (RNFL) was measured from the internal limiting membrane to the RNFL posterior boundary after removing large vessels with a radial peripapillary capillary slab. The whole en-face image small vessel density in optic disc OCTA scans was measured in the entire 4.5 × 4.5 mm image centered on the optic disc, and peripapillary small vessel density was calculated in the region of the 750 μm wide elliptical annulus extending from the optic disc boundary. The whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels, as measured by the OCTA software, were recorded as percentages (Figure 1).

The study was performed per the Principles of the Declaration of Helsinki, and approval was obtained from the local ethics committee before starting the study. Informed consent was obtained from all individual participants included in this study. This study was supported by the research fund of SANKO University (Project no. is TF.AP.2021/01).

Statistical analysis

Sociodemographic and clinical characteristics are presented as descriptive statistics. As descriptive statistics, mean and standard deviation (SD) values were given for quantitative data and number and percentage values for qualitative data. The normality of the distribution of continuous variables was tested by the Shapiro–Wilk test. In the comparison of groups, the independent-samples t-test was used for quantitative data and the chi-square test for qualitative data. The paired-samples t-test (for normally distributed data) and the Wilcoxon test (for non-normally distributed data) were applied for intra-group comparisons. The independent-sample t-test (for normally distributed data) and the Mann–Whitney U test (for non-normally distributed data) were used to compare numerical variables between groups. Spearman correlation was used to investigate the relationship between the variables. Statistical analysis was performed by SPSS for Windows, version 25.0, and a p-value of <0.05 was considered statistically significant.

RESULTS

This study included 54 eyes of 27 patients with migraine (21 female and 6 male patients) with a mean age of 30.22 ± 7.86 years (range = 18-46). Twelve (44.4%) of the patients had migraine with aura (MwA) and fifteen (55.6%) had migraine without aura (MwoA). The sociodemographic data of the participants are provided in Table 1, and the self-reported clinical features of the headache are presented in Tables 2 and 3.

According to the self-reported data provided by patients during their initial presentation, the frequency of headaches experienced within the preceding three months was as follows: 4 (14.8%) individuals reported daily, 11 (40.7%) 2-3 times per week, 1 (3.7%) once per week, 8 (29.6%) 1-2 times per month, while 3 (11.1%) 1-2 times in a 2-3 month period. However, upon follow-up, it was determined that none of the patients experienced pain for more than 15 days per month. So none were diagnosed as chronic migraine. There were no significant differences between the sociodemographic and clinical features of patients with migraine with and without aura. Comorbid conditions in the patient with MwoA were asthma, thyroid disease, and hypertension. In the patient with MwA, the comorbidities were celiac disease and thyroid disease.

The intraocular pressure and central corneal thickness values of the patients are shown in Table 4.

The whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels assessed by OCTA revealed no statistically significant differences between the ictal and

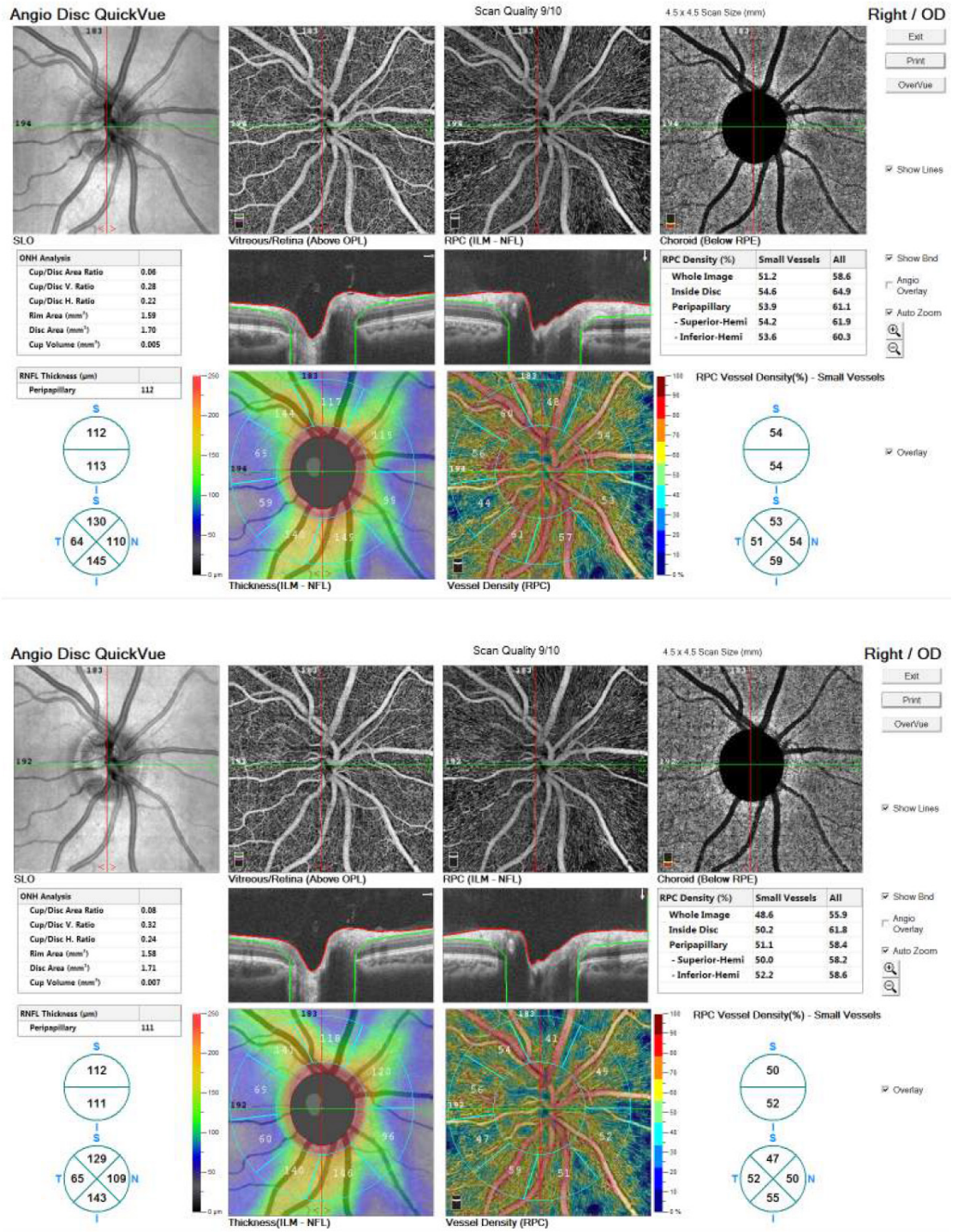

Figure 1. OCTA images of a patient with MwA, ictal (above) and interictal (below).

interictal periods in 54 eyes of 27 patients (for all, p>0.05) (Table 5).

In the subgroup analyses, no statistically significant differences were observed in the whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels (as measured by OCTA) between the ictal and interictal periods patients with migraine with and without aura (for all, p>0.05) (Table 6).

Table 1: Sociodemographic data of the patients with migraine with and without aura

	MwA n(%)	MwoA n(%)	p
Age			
Mean±SD (min-max)	28.92±8.32 (18-45)	31.27±7.60 (22-46)	0.451
Gender			
Male	3 (25.0)	3 (20.0)	> 0.999
Female	9 (75.0)	12 (80.0)	
Marital status			
Married	5 (41.7)	8 (53.3)	0.830
Single	7 (58.3)	7 (46.7)	
Educational status			
No formal education	1 (8.3)	0	
Primary school	0	2 (13.3)	
Middle school	1 (8.3)	2 (13.3)	0.643
High school	3 (25.0)	2 (13.3)	
University and higher	7 (58.3)	9 (60.0)	
Alcohol consumption			
Yes	1 (8.3)	3 (20.0)	0.605
No	11 (91.7)	12 (80.0)	
Smoking			
Yes	3 (25.0)	4 (26.7)	> 0.999
No	9 (75.0)	11 (73.3)	
Comorbid disease			
Yes	3 (25.0)	5 (33.3)	0.696
No	9 (75.0)	10 (66.7)	

MwA: Migraine with aura, MwoA: Migraine without aura; n:number

Table 2: Self-reported clinical features of headache in patients with migraine with and without aura

	MwA n(%)	MwoA n(%)	p
Lost productive time due to headache			
No	1 (8.3)	0	
A few days a week	5 (41.7)	7 (46.7)	0.909
A few days a month	6 (50.0)	7 (46.7)	
Less frequent	0	1 (6.7)	
Attack severity			
Very severe	6 (50.0)	10 (66.7)	
Severe	4 (33.3)	3 (20.0)	0.758
Tolerable	2 (16.7)	2 (13.3)	
Duration of attacks			
4-24 hours	6 (50.0)	8 (53.3)	
2-3 days	5 (41.7)	6 (40.0)	> 0.999
4-7 days	1 (8.3)	1 (6.7)	
Time of onset of headache			
1 year	3 (25.0)	1 (6.7)	
2-3 years	2 (16.7)	1 (6.7)	
4-5 years	1 (8.3)	4 (26.7)	0.384
6-10 years	3 (25.0)	2 (13.3)	
More than 10 years	3 (25.0)	7 (46.7)	
Pain location			
Right	1 (8.3)	2 (13.3)	
Left	3 (25.0)	3 (20.0)	> 0.999
Right or Left	8 (66.7)	7 (46.7)	
Unknown (missing)	0	3 (20.0)	

MwA: Migraine with aura, MwoA: Migraine without aura; n:number

Table 3: Self-reported headache provoking factors and their accompanying findings

	MwA (n=12) n (%)		MwoA (n=15) n (%)		p
Provoking factors					
Aggressiveness	9 (75.0)		12 (80.0)		> 0.999
Sadness	11 (91.7)		13 (86.7)		> 0.999
Fatigue	12 (100.0)		9 (60.0)		0.020
Changes in sleep patterns	11 (91.7)		12 (80.0)		0.605
Menstruation	7 (58.3)		10 (66.7)		0.706
Food/Diet	5 (41.7)		7 (46.7)		> 0.999
Medication	1 (8.3)		0 (0.0)		0.444
Holding the head steady	7 (58.3)		7 (46.7)		0.830
Heavy exercise	6 (50.0)		2 (13.3)		0.087
Cough	3 (25.0)		4 (26.7)		> 0.999
Accompanying findings					
Palpitation	6 (50.0)		4 (26.7)		0.257
Abdominal pain	4 (33.3)		1 (6.7)		0.139
Sweating/chills	12 (100.0)		9 (60.0)		0.020
Diarrhea	1 (8.3)		0 (0.0)		0.444
Mood change	12 (100.0)		13 (86.7)		0.487
Distractibility	11 (91.7)		11 (73.3)		0.342
Eye pain	9 (75.0)		12 (80.0)		> 0.999
Tearing	7 (58.3)		4 (26.7)		0.130
Blurred vision	9 (75.0)		8 (53.3)		0.424
	Sometimes	**Always**	**Sometimes**	**Always**	
Voice sensitivity	1 (8.3)	10 (83.3)	2 (13.3)	12 (80.0)	> 0.999
Light sensitivity	2 (16.7)	10 (83.3)	1 (6.7)	14 (93.3)	0.569
Nausea	4 (33.3)	6 (50.0)	3 (20.0)	12 (80.0)	0.139
Vomiting	2 (16.7)	3 (25.0)	7 (46.7)	2 (13.3)	0.347

MwA: Migraine with aura, MwoA: Migraine without aura; n:number

Ictal and interictal OCTA images of a patient with MwA are shown in Figure 1. Figure 2 shows the ictal and interictal OCTA images of a patient with MwoA.

Furthermore, no significant differences were observed in OCTA-measured the whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels between smokers and non-smokers (for all, p>0.05) (Table 7).

In addition, the OCTA-measured the whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels were compared

Table 4: Intraocular pressure and central corneal thickness measurements

	MwA (n=12) Mean±SD	MwoA (n=15) Mean±SD	p
Intraocular pressure (mm Hg) Right eye	16.91±3.75	16.93±3.49	0.991
Intraocular pressure (mm Hg) Left eye	17.00±3.56	16.53±2.97	0.714
Central corneal thickness (μm) Right eye	553.16±35.73	540.33±25.86	0.289
Central corneal thickness (μm) Left eye	555.00±34.62	539.86±26.47	0.209

MwA: Migraine with aura, MwoA: Migraine without aura, Mean±SD: Mean±standard deviation, n:number

Table 5: Comparison of RPC vessel density results measured by OCTA in migraine patients during the ictal and interictal periods

	Right Eye Ictal n=27	Right Eye Interictal n=27	p	Left Eye Ictal n=27	Left Eye Interictal n=27	p
SMALL VESSELS						
RPC whole image, %	50.64±2.35	51.00±2.11	0.455[b]	51.06±1.92	51.15±2.04	0.832[b]
RPC inside disc, %	50.20 (32.70-59.20)	52.40 (34.70-60.00)	0.116[a]	51.19±4.82	50.42±5.57	0.392[b]
RPC peripapillary, %	53.49±2.95	53.68±2.57	0.765[b]	53.50 (49.10-59.20)	53.80 (30.50-59.90)	0.423[a]
RPC superior-hemi, %	53.55±3.16	53.94±2.69	0.583[b]	53.96±2.65	54.50±2.84	0.322[b]
RPC inferior-hemi, %	53.41±3.12	53.41±2.82	1.000[b]	52.95±2.83	53.07±2.34	0.817[b]
ALL						
RPC whole Image, %	57.46±2.41	57.85±2.14	0.375[b]	57.79±1.95	57.84±2.00	0.893[b]
RPC inside disc, %	60.40 (43.70-67.10)	63.00 (46.60-68.50)	0.127[a]	61.12±3.81	60.48±4.69	0.384[b]
RPC peripapillary, %	60.08±2.85	60.40±2.53	0.592[b]	60.05±2.50	60.24±2.31	0.673[b]
RPC superior-hemi, %	60.38±2.85	60.82±2.58	0.487[b]	0.62±2.67	60.92±2.73	0.542[b]
RPC inferior-hemi, %	59.76±3.06	59.96±2.68	0.731[b]	59.41±2.55	59.49±2.20	0.846[b]

RPC: Radial peripapillary capillary segment; [a]Wilcoxon Test [median (min-max)]; [b]Paired-samples T test (mean±SD); n: number

Table 6: Comparison of RPC vessel density results measured by OCTA according to migraine type

OCTA parameter	MwA (n=12)		MwoA (n=15)		p	
	ictal period	interictal period	ictal period	interictal period	ictal	interictal
SMALL VESSELS						
RPC Whole Image, %						
Right eye	50.02±1.81	50.46±2.33	51.14±2.66	51.42±1.89	0.226	0.249
Left eye	50.86±1.54	50.83±2.03	51.22±2.22	51.40±2.09	0.638	0.481
RPC Inside Disc, %						
Right eye	49.01±7.18	49.85 (34.70-60.00)	51.32±5.21	53.60 (47.60-58.10)	0.342	0.083[a]
Left eye	50.12±5.24	49.88±5.68	52.04±4.46	50.86±5.64	0.313	0.658
RPC Peripapillary, %						
Right eye	52.85±2.33	53.70 (48.70-57.00)	54.00±3.36	53.80 (51.00-59.50)	0.322	0.399[a]
Left eye	53.12±2.04	53.25±1.97	53.80±2.83	52.94±6.63	0.492	0.874
RPC Superior-Hemi, %						
Right eye	52.72±2.28	53.28±2.67	54.22±3.66	54.48±2.68	0.229	0.260
Left eye	53.80±1.92	54.20±2.51	54.09±3.18	54.74±3.15	0.788	0.629
RPC Inferior-Hemi, %						
Right eye	52.96±2.93	53.20±2.96	53.76±3.32	53.57±2.80	0.519	0.746
Left eye	52.35±2.74	52.22±2.13	53.43±2.90	53.74±2.34	0.334	0.094
ALL						
RPC Whole Image, %						
Right eye	57.05±2.03	57.40±2.25	57.79±2.70	58.20±2.05	0.438	0.346
Left eye	57.72±1.67	57.60±1.95	57.85±2.19	58.03±2.10	0.869	0.595

RPC Inside Disc, %						
Right eye	61.00 (43.70-66.50)	58.80 (46.60-68.50	60.40 (50.40-67.10)	63.50 (54.50-66.00)	0.719[a]	0.114[a]
Left eye	59.95±4.44	59.59±5.01	62.07±3.06	61.20±4.47	0.155	0.385
RPC Peripapillary, %						
Right eye	59.68±2.45	59.94±2.79	60.41±3.18	60.77±2.33	0.520	0.407
Left eye	59.85±2.19	59.80±1.87	60.22±2.78	60.59±2.62	0.711	0.387
RPC Superior-Hemi, %						
Right eye	59.82±2.26	60.17±2.73	60.84±3.25	61.34±2.42	0.368	0.249
Left eye	60.56±2.17	60.61±2.34	60.68±3.09	61.18±3.06	0.915	0.604
RPC Inferior-Hemi, %						
Right eye	59.51±2.87	59.70±2.99	59.96±3.29	60.17±2.49	0.716	0.663
Left eye	59.05±2.55	58.92±1.92	59.69±2.61	59.94±2.36	0.532	0.238

Independent-samples T test (mean±SD); [a]Mann-Whitney U test [median (min-max)]. MwA:Migraine with aura, MwoA:Migraine without aura; RPC:Radial peripapillary capillary segment; Mean±SD: Mean±standard deviation, n:number. Ictal and interictal OCTA images of a patient with MwA are shown in Figure 1. Figure 2 shows the ictal and interictal OCTA images of a patient with MwoA.

between men and women. The whole-image, peripapillary, superior-hemi vessel density of the RPC of the small vessels were significantly higher in female than male in both right and left eyes in the ictal period (p=0.041, p=0.029, p=0.025, p=0.036, p=0.049, p=0.034, respectively). The inferior-hemi vessel density of the RPC of the small vessels and whole-image, peripapillary vessel density of the RPC of the all vessels were significantly higher in female than male in right eyes in the ictal period (p=0.026, p=0.044, p=0.047, respectively). In the interictal period; the peripapillary, superior-hemi vessel density of the RPC of the small and all vessels were significantly higher in female than male in left eyes (p=0.002, p=0.003, p=0.040, p=0.018, respectively) (Table 8).

No correlation was observed between the whole-image, inside-disc, peripapillary, superior-hemi, and inferior-hemi vessel density of the RPC of the small vessels and all vessels assessed by OCTA and the severity, duration, and frequency of attacks (for all, p>0.05) (Table 9).

DISCUSSION

In the current study, vessel density in the RPC as assessed by OCTA did not differ between the ictal and interictal periods in migraine patients. As well, the subgroup analysis revealed similar vessel densities in the RPC values in MwA and MwoA cases for both ictal and interictal OCTA imaging. To the best of our knowledge, except for case reports[14,15], this is the first study to evaluate the ocular vascular network with OCTA in the ictal and interictal periods in the same cohort consisting of patients with migraine. In previous studies, OCTA findings of patients with migraine with and without aura have mostly been compared with those of controls.[10-12] However, these studies evaluated the vascular density in different areas and thus reported diverse results.[10]

A study that compared the OCTA findings of the parafoveal superficial vessel density in 38 eyes of 19 patients with MwA and 38 eyes of 19 healthy participants reported similar results in both groups.[16] Another study involving 38 patients with migraine and 32 controls evaluated central macular vascular and optic disc perfusion and reported no differences between the groups.[12] Moreover, a study that compared the OCTA findings of patients with migraine with and without aura and controls reported similar foveal, perifoveal, parafoveal, and whole-area vessel density in all three groups.[17] In addition, a previous study reported no differences in retinal vessel density in MwA compared with MwoA; however, the study did report a decrease in foveal choriocapillaris vessel density.[18]

In another study, 15 patients with MwA, 12 patients with MwoA, and 22 controls were evaluated for macular and optic nerve measurements by OCTA. The authors found a decrease in the superior peripapillary vessel density in the MwA group but did not observe differences in the whole image, optic nerve, total peripapillary, or inferior peripapillary vessel densities.[11] Another study compared the vessel density of the optic nerve head, RPC segment, superficial macular area, and deep macular area

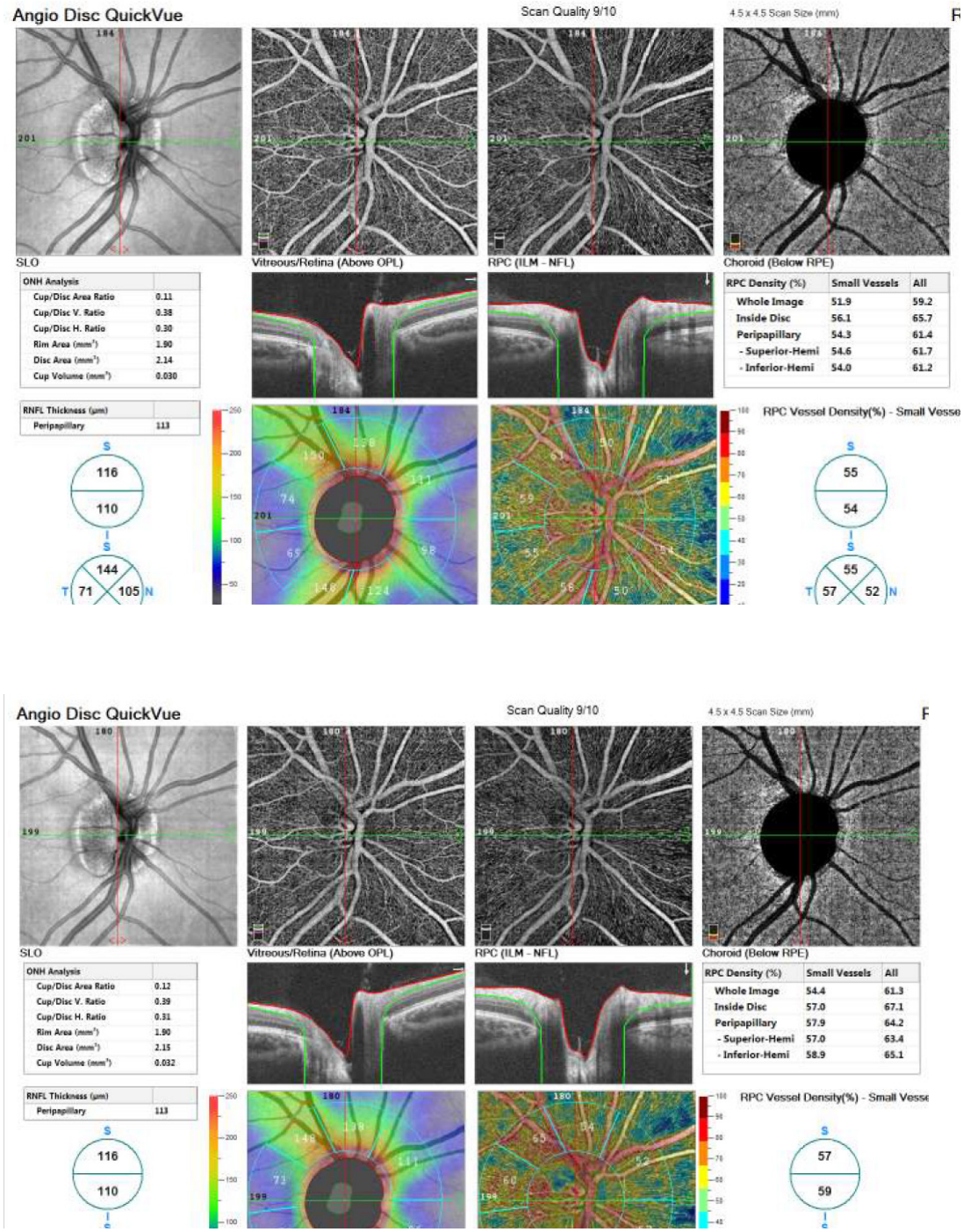

Figure 2. OCTA images of a patient with MwoA, ictal (above) and interictal (below).

between a migraine group and a control group; the results revealed decreased vessel density measurements in the nasal and inferotemporal optic nerve head, inferonasal RPCs, and the deep macular plexus of patients with MwA.[19]

One study reported that vessel densities in the superficial and deeper retinal foveal, whole optic disc, inside disc, peripapillary, superior hemisphere, and superior and temporal layers were significantly lower in migraine patients compared with healthy controls regardless of the presence of aura.[20] However, in a study on patients

Table 7: Comparison of RPC vessel density results measured by OCTA in the smokers and non-smokers patients with migraine

OCTA parameter	Smoker (n=7)		Non-smoker (n=20)		p	
	ictal period	interictal period	ictal period	interictal period	ictal	interictal
SMALL VESSELS						
RPC Whole Image, %						
Right eye	49.70±2.71	50.77±2.15	50.98±2.19	51.08±2.15	0.223	0.747
Left eye	50.12±2.62	50.60±1.29	51.39±1.56	51.34±2.24	0.137	0.418
RPC Inside Disc, %						
Right eye	48.70±5.65	52.00 (43.80-57.30)	50.86±6.35	52.75 (34.70-60.00)	0.435	0.850 [a]
Left eye	51.21±5.64	51.08±4.82	51.18±4.67	50.20±5.91	0.989	0.725
RPC Peripapillary, %						
Right eye	52.14±3.02	53.22±2.77	53.96±2.85	53.84±2.55	0.165	0.596
Left eye	52.70±3.56	52.40 (51.40-57.50)	53.78±2.04	54.15 (30.50-59.90)	0.332	0.198 [a]
RPC Superior-Hemi, %						
Right eye	52.64±3.18	53.62±3.06	53.87±3.17	54.06±2.63	0.386	0.723
Left eye	53.22±4.13	53.91±3.05	54.22±1.99	54.71±2.82	0.404	0.535
RPC Inferior-Hemi, %						
Right eye	51.61±3.23	52.78±2.73	54.04±2.90	53.63±2.89	0.077	0.507
Left eye	52.11±3.66	52.25±2.46	53.24±2.53	53.39±2.27	0.374	0.238
ALL						
RPC Whole Image, %						
Right eye	56.31±2.83	57.54±2.38	57.86±2.18	57.96±2.10	0.147	0.666
Left eye	56.75±2.86	57.21±1.51	58.16±1.43	58.06±2.14	0.102	0.345
RPC Inside Disc, %						
Right eye	59.40 (52.60-65.40)	62.20 (56.90-66.00)	61.60 (43.70-67.10)	63.25 (46.60-68.50)	0.288 [a]	0.978 [a]
Left eye	61.10±4.53	61.18±3.41	61.14±3.66	60.24±5.12	0.982	0.657
RPC Peripapillary, %						
Right eye	58.60±3.13	59.81±2.87	60.61±2.63	60.61±2.45	0.110	0.485
Left eye	59.20±3.78	59.35±2.09	60.35±1.91	60.55±2.36	0.302	0.249
RPC Superior-Hemi, %						
Right eye	59.21±3.19	60.38±3.12	60.80±2.68	60.98±2.43	0.211	0.610
Left eye	59.80±4.14	60.08±2.54	60.92±2.00	61.22±2.79	0.350	0.353
RPC Inferior-Hemi, %						
Right eye	57.91±3.17	59.22±2.68	60.41±2.82	60.22±2.70	0.062	0.408
Left eye	58.54±3.78	58.60±2.40	59.71±2.01	59.80±2.10	0.305	0.219

Independent-samples T test (mean±SD); [a]Mann-Whitney U test [median (min-max)]. RPC:Radial peripapillary capillary segment.

with migraine with visual aura, OCTA revealed decreased superficial and deep foveal, whole optic disc, peripapillary, superior hemisphere, inferior hemisphere, superior quadrant, and temporal quadrant vascular densities.[21]

In another study that assessed vessel and perfusion density of both the macula and optic nerve head, the vessel and perfusion density in the macula decreased in migraine patients with and without aura, but vessel density in the optic nerve head decreased only in migraine patients with aura, and the results showed no differences in

Table 8: Comparison of RPC vessel density results measured by OCTA according to gender

OCTA parameter	Female (n=21)		Male (n=6)		p	
	ictal period	interictal period	ictal period	interictal period	ictal	interictal
SMALL VESSELS						
RPC Whole Image, %						
Right eye	51.13±2.39	51.19±2.13	48.93±1.17	50.33±2.11	0.041*	0.393
Left eye	51.49±1.78	51.54±2.02	49.58±1.76	49.76±1.58	0.029*	0.059
RPC Inside Disc, %						
Right eye	50.15±6.01	52.40 (34.70-60.00)	50.81±7.17	53.60 (48.90-58.10)	0.821	0.376 [a]
Left eye	51.34±4.64	50.14±5.44	50.65±5.87	51.43±6.43	0.762	0.626
RPC Peripapillary, %						
Right eye	54.16±3.00	53.97±2.59	51.15±0.94	52.66±2.44	0.025*	0.281
Left eye	54.03±2.33	54.20 (30.50-59.90)	51.65±2.28	51.65 (49.70-52.80)	0.036*	0.002[a]*
RPC Superior-Hemi, %						
Right eye	54.1±3.23	54.27±2.65	51.33±1.59	52.81±2.76	0.049*	0.252
Left eye	54.53±2.35	55.32±2.46	51.96±2.87	51.61±2.23	0.034*	0.003*
RPC Inferior-Hemi, %						
Right eye	54.11±3.18	53.68±2.97	50.95±0.87	52.46±2.19	0.026*	0.364
Left eye	53.43±2.75	53.50±2.28	51.25±2.64	51.53±1.98	0.096	0.067
ALL						
RPC Whole Image, %						
Right eye	57.95±2.40	58.00±2.19	55.73±1.64	57.33±2.05	0.044*	0.512
Left eye	58.14±1.88	58.17±2.01	56.56±1.80	56.70±1.65	0.079	0.115
RPC Inside Disc, %						
Right eye	60.20 (43.70-67.10)	63.00 (46.60-68.50)	61.20 (52.60-65.40)	63.20 (57.90-66.00)	0.887[a]	0.512[a]
Left eye	61.26±3.71	60.23±4.68	60.66±4.50	61.38±5.09	0.743	0.607
RPC Peripapillary, %						
Right eye	60.66±2.89	60.59±2.63	58.06±1.58	59.75±2.24	0.047*	0.484
Left eye	60.44±2.44	60.72±2.34	58.70±2.40	58.55±1.25	0.135	0.040*
RPC Superior-Hemi, %						
Right eye	60.90±2.90	61.01±2.65	58.60±1.85	60.16±2.43	0.081	0.489
Left eye	61.07±2.60	61.57±2.61	59.08±2.53	58.66±1.90	0.110	0.018*
RPC Inferior-Hemi, %						
Right eye	60.40±3.11	60.15±2.84	57.50±1.44	59.31±2.11	0.037*	0.512
Left eye	59.72±2.44	59.78±2.22	58.30±2.86	58.46±1.95	0.234	0.202

Independent-samples T test (mean±SD); [a]Mann-Whitney U test [median (min-max)]. RPC:Radial peripapillary capillary segment.
*significant at $p < 0.05$

the perfusion density. The authors suggested that this was related to the autoregulation mechanism of the optic disc and that retinal perfusion in patients with migraine would not be altered in the autoregulation range.[22]

One study comparing OCTA measurements of patients with migraine in the ictal period with those of a control group suggested that an acute migraine attack does not affect retinal or peripapillary blood flow.[23] In a case report, the

Table 9: Correlations between the RPC vessel density and the severity, duration, and frequency of attacks

OCTA parameters			Severity of attacks	Duration of attacks	Frequency of attacks
SMALL VESSELS					
RPC Whole Image, %					
Right eye	ictal period	r	-0.120	0.080	-0.048
		p	0.552	0.693	0.812
	interictal period	r	-0.257	0.151	-0.230
		p	0.197	0.452	0.249
Left eye	ictal period	r	-0.039	0.359	-0.081
		p	0.848	0.066	0.686
	interictal period	r	0.033	0.196	-0.158
		p	0.871	0.326	0.431
RPC Inside Disc, %					
Right eye	ictal period	r	0.092	-0.116	-0.029
		p	0.648	0.564	0.887
	interictal period	r	0.031	-0.279	0.144
		p	0.877	0.158	0.475
Left eye	ictal period	r	0.058	0.021	0.096
		p	0.774	0.918	0.635
	interictal period	r	-0.080	-0.037	-0.292
		p	0.690	0.855	0.139
RPC Peripapillary, %					
Right eye	ictal period	r	-0.054	0.126	-0.005
		p	0.790	0.530	0.981
	interictal period	r	-0.216	0.225	-0.239
		p	0.279	0.259	0.229
Left eye	ictal period	r	-0.047	0.329	-0.115
		p	0.816	0.094	0.568
	interictal period	r	0.039	0.361	-0.077
		p	0.847	0.064	0.704
RPC Superior-Hemi, %					
Right eye	ictal period	r	-0.042	0.162	-0.096
		p	0.837	0.420	0.634
	interictal period	r	-0.189	0.129	-0.221
		p	0.345	0.521	0.269
Left eye	ictal period	r	-0.024	0.320	-0.120
		p	0.906	0.104	0.552
	interictal period	r	0.097	0.252	-0.034
		p	0.629	0.204	0.868
RPC Inferior-Hemi, %					
Right eye	ictal period	r	-0.071	0.153	< 0.001
		p	0.725	0.445	> 0.999
	interictal period	r	-0.243	0.201	-0.215
		p	0.222	0.316	0.281
Left eye	ictal period	r	-0.007	0.276	-0.067
		p	0.974	0.163	0.740
	interictal period	r	0.140	0.318	-0.019
		p	0.486	0.106	0.924

ALL					
RPC Whole Image, %					
Right eye	ictal period	r	-0.073	0.105	-0.148
		p	0.716	0.601	0.460
	interictal period	r	-0.281	0.147	-0.292
		p	0.155	0.465	0.139
Left eye	ictal period	r	-0.007	0.314	-0.201
		p	0.972	0.111	0.314
	interictal period	r	-0.007	0.264	-0.192
		p	0.971	0.183	0.338
RPC Inside Disc, %					
Right eye	ictal period	r	0.099	-0.066	-0.072
		p	0.624	0.742	0.722
	interictal period	r	0.081	-0.116	0.034
		p	0.689	0.566	0.868
Left eye	ictal period	r	0.067	0.097	0.086
		p	0.741	0.631	0.669
	interictal period	r	-0.141	-0.051	-0.316
		p	0.482	0.801	0.108
RPC Peripapillary, %					
Right eye	ictal period	r	-0.050	0.181	-0.101
		p	0.803	0.367	0.618
	interictal period	r	-0.220	0.185	-0.278
		p	0.269	0.357	0.161
Left eye	ictal period	r	0.014	0.260	-0.211
		p	0.943	0.190	0.292
	interictal period	r	0.019	0.317	-0.134
		p	0.925	0.107	0.505
RPC Superior-Hemi, %					
Right eye	ictal period	r	-0.035	0.144	-0.158
		p	0.863	0.473	0.431
	interictal period	r	-0.157	0.131	-0.239
		p	0.434	0.515	0.229
Left eye	ictal period	r	0.028	0.245	-0.182
		p	0.890	0.218	0.363
	interictal period	r	0.109	0.242	-0.043
		p	0.587	0.224	0.831
RPC Inferior-Hemi, %					
Right eye	ictal period	r	-0.087	0.197	-0.105
		p	0.665	0.324	0.601
	interictal period	r	-0.293	0.156	-0.364
		p	0.139	0.438	0.062
Left eye	ictal period	r	0.027	0.231	-0.221
		p	0.892	0.247	0.269
	interictal period	r	0.052	0.304	-0.249
		p	0.796	0.123	0.210

Spearman correlation

right eye of a patient with visual aura presented diffuse narrowing of the retinal vessels, decreased RPC density, and decreased superficial and deep foveal vessel density during the attack, with subsequent improvements in these changes.[14] In another migraine case with visual aura, a large area of hypoperfusion was reported in the macular region of the right eye; this returned to normal in the follow-ups.[15] Although our study observed no differences between patients with migraine with and without aura, we did not perform OCTA in the aura phase in these cases. Further studies performing OCTA during the aura phase may provide more information.

When we compared the vessel densities in OCTA measurements according to gender, we found that the vessel density in some areas was higher in females. In a previous study conducted on normal eyes, peripapillary vessel density was higher in females, but the reason for this was unclear.[24] Estrogen may affect ocular vascularity and may be protective against retinal ischemia in women of reproductive age.[25,26]

Previous studies that evaluated the features of migraine attacks according to OCTA findings reported conflicting results.[18,21,22,27] In the present study, we did not find any correlations between vessel density measurements according to OCTA and any of the clinical features.

One of the limitations of our study is the small sample size. An advantage of our study is that measurements were conducted in the ictal and interictal periods in the same cohort. However, the data obtained with OCTA are cross-sectional, and migraine attacks may vary in the same person; thus, a single attack may not provide sufficient information. There is still no consensus on what should be assessed on OCTA in patients with migraine. Studies in this area may provide insight into which vascular parameters should be assessed in migraine. In addition, prospective follow-up studies could be performed to investigate the correlations between OCTA changes and the clinical features of attacks. Evaluations performed during the aura period may also provide valuable data.

In the present study, we did not find any differences in the RPC vessel density between the ictal and interictal periods of migraine and also between migraine cases with and without aura. On one hand, our results may indicate that the measurement of vessel density in the RPC segment alone does not contribute to the understanding of the vascular pathophysiology of migraine. Also, migraine attacks may not have a direct impact on the retinal peripapillary capillary vessel density and OCTA may not be an appropriate tool for evaluating the vascular changes in migraine.

However, on the other hand, we do not have OCTA protocols for migraine research, yet. The results of previous OCTA studies on patients with migraine have been inconsistent, that may be due to differences in the study design and the vascular parameters measured by OCTA and/or differences in the technical characteristics of the devices. We propose that the protocols for OCTA use in patients with migraine should be clarified to homogenize study designs and improve data collection.

DISCLOSURE

Financial support: This study was supported by the research fund of SANKO University (Project no. is TF.AP.2021/01).

Conflict of interest: None

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