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Quantitative analysis of vessel density in the optic disc and macular of patients with idiopathic optic neuritis

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特发性视神经炎患者视盘及黄斑区血流密度的定量研究

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摘要

目的:评估特发性视神经炎(ON)患者的患眼和未受累对侧眼的视盘及黄斑的血流密度改变情况,为特发性 ON 的治疗和随访提供一定的临床指导。

方法:横断面研究。收集 2019-12/2021-12 于扬州大学附属苏北人民医院眼科确诊的初次发病且病程≤3 mo 的单眼特发性 ON 患者 16 例,分为患眼组 16 眼与未受累对侧眼组 16 眼,另收集性别、年龄相匹配的健康者 20 例 20 眼作为对照组。所有眼均行视盘区 4.5 mm×4.5 mm 及黄斑区 6 mm×6 mm 光相干断层扫描血管成像(OCTA)检查,收集视盘区及黄斑区各血流指标,并对三组间各指标进行对比及分析。

结果:与对照组及未受累对侧眼组相比,ON 患眼组视盘全区域及视盘周围各分区毛细血管、全部血管血流密度均降低($P<0.05$)。与未受累对侧眼组相比,ON 患眼黄斑区整体及中心凹周围全部分区 SCP 血流密度均显著降低($P<0.05$),旁中心凹 SCP 血流密度仅在上半侧及上侧分区显著降低($P<0.05$)。与对照组相比,ON 患眼组黄斑中心凹周围下半侧、鼻侧、下侧 SCP 密度降低(均 $P<0.05$)。与对照组相比,未受累对侧眼组黄斑区整体及各分区 SCP 血流密度均增加($P<0.05$),旁中心凹 SCP 血流密度增加($P<0.05$),但下半侧、鼻侧分区改变无统计学差异($P>0.05$),中心凹周围 SCP 血流密度增加仅在上半侧及上侧分区有统计学意义($P<0.05$)。

结论:病程 3 mo 以内的 ON 患者会出现视盘周围各分区血管密度的降低和黄斑中心凹周围部分分区 SCP 血流密度的降低,同时伴随着对侧眼黄斑区部分分区的 SCP 血流密度的增加。

关键词:视神经炎;光相干断层扫描血管成像;视盘血流;黄斑血流

Abstract

• AIM: To assess the changes of vessel density in the optic disc and macular of the affected eye and the uninvolved contralateral eye in patients with idiopathic optic neuritis (ON) and to provide clinical guidance for the treatment and follow-up of idiopathic ON.

• METHODS: A total of 16 patients with first-episode monocular idiopathic ON ≤ 3 mo diagnosed between December 2019 and December 2021 were included in this cross-sectional study. The eye of patients was divided into 16 eyes in the affected eye group and 16 eyes in the uninvolved contralateral eye group, and 20 healthy age-matched eyes (n= 20) served as controls. Optical coherence tomography angiography (OCTA) was performed in all eyes at 4.5 mm×4.5 mm region of the optical disc and 6 mm×6 mm region of the macular, and blood flow indicators were collected and compared.

• RESULTS: Compared with the control group and the uninvolved contralateral eye group, the density of all vessels and capillary were reduced in the whole area of optic disc, and all subdivisions of the peripapillary region in the ON group (all $P<0.05$). Compared with the uninvolved contralateral eye group, the density of superficial capillary plexus (SCP) was significantly lower in the whole area of macular and perifovea region, and its all subdivisions of the ON eye, as well as in the superior-hemi and superior subdivision of the parafovea region (all $P<0.05$). Compared with the control group, the density of SCP in the inferior-hemi, nasal, and inferior perifovea region was significantly reduced in the ON affected eye group (all $P<0.05$). Compared with the control group, the whole area of macular and its subdivisions in the uninvolved contralateral eye group showed an increase in the density of SCP ($P<0.05$) and an increase in the density of SCP in the parafovea region ($P<0.05$), but no significant change in the inferior-hemi and nasal subdivisions; the increase in the density of SCP in the perifovea region was only significant in the superior-hemi

and superior subdivisions ($P<0.05$).

• CONCLUSION: Patients with ON in the duration of ≤3 mo may showed a decreased vessel density in all peripapillary subdivisions, and a decreased density of SCP in some subdivisions of the perifovea region, accompanied by an increased density of SCP in some subdivisions of the macular region of the contralateral eyes.

• KEYWORDS: optic neuritis; optical coherence tomography angiography; optic disc; macular blood flow
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INTRODUCTION

Optic neuritis (ON) is a condition that includes a variety of inflammatory lesions involving the optic nerve, most commonly affecting young and middle-aged people.ON can be classified as demyelinating optic neuritis (DON), infectious and infection - related, autoimmune, and another unclassifiable form, depending on the cause. DON includes idiopathic demyelinating optic neuritis (IDON), multiple sclerosis-related optic neuritis (MS-ON), neuromyelitis optica-related optic neuritis (NMO-ON). MS-ON is self-healing and is the most common type of ON reported in European and American studies, unlike NMO-ON, which causes quick and severe diminution of vision with poor prognosis and is commonly reported in Asian countries[1-2].

Optical coherence tomography angiography (OCTA) is a new non-invasive vascular imaging technique that can detect blood flow changes in the retina in layers. Kurtul *et al*[3] suggested OCTA may be suggested for use in follow-up and management of pediatric migraine patients. The results of several studies based on MS and NMO have shown that the vessel density in the optic disc and macular is reduced in MS and NMO patients; however, patients with ON have lower blood flow density than those without ON, which suggests that changes in retinal blood perfusion accompany ON. A correlation was also reported between the reduction in vessel density and retinal structure and visual function[4-10]. More recently, it has been found that vessel density is reduced in localized areas of the optic disc and macular in the uninvolved contralateral eye of patients with ON compared to the healthy control group[11]. However, these studies have mainly focused on patients with ON disease lasting >6 mo, and there is a lack of research on whether the optic disc and macular vessel density are altered in patients with ON disease lasting ≤3 mo.

The present study focused on patients with first-episode idiopathic ON in the duration of ≤3 mo. Their uninvolved contralateral eyes were included in the study to investigate the changes in vessel density of optic disc and the macular between the ON affected eye group, the uninvolved contralateral eye group, and the healthy control group.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the Medical Ethics Committee of Northern Jiangsu People's Hospital, Yangzhou University (No. 2021ky317); all subjects fully understood the purpose and methods of the study and signed the informed consent form. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Study Subjects This cross-sectional study included 16 patients with idiopathic ON in one eye who attended the Ophthalmology Department of Northern Jiangsu People's Hospital between September 2019 and December 2021. Patients were diagnosed with the condition for the first time by two experienced ophthalmologists according to the Expert Consensus on the Diagnosis and Treatment of Optic Neuritis (2014)[2], who established that the duration of the disease was ≤ 3 mo. They were divided into 16 eyes ($n=16$) in the affected eye group and 16 eyes ($n=16$) in the uninvolved contralateral eye group. In addition, 20 healthy eyes ($n=20$), matched with the ON patients by gender and age, were included as a control group. Exclusion criteria for the ON group were the followings: 1) patients with recurrent ON; 2) patients with disease duration of >3 mo; 3) patients with infectious and infection-related (tuberculosis, syphilis, *etc.*), autoimmune ON (Systemic lupus erythematosus, Sjogren's syndrome, *etc.*); 4) malignant tumors or ocular pathologies that may affect visual function, including retinal disease and optic nerve diseases, such as diabetic retinopathy, glaucoma, ischemic optic neuropathy, and compressive optic nerve disease; 5) history of neurological impairment or neuropathy diagnosed prior to the first ON (*e.g.*, NMOSD or MS); 6) history of ocular surgery and trauma; 7) absolute refractive error ≥ 6.0 D; 8) intraocular pressure > 21 mmHg or bilateral ocular pressure difference >5 mmHg; 9) refractive media clouding, resulting in an OCTA image signal quality index <6. Inclusion criteria for the control group were as follows: 1) healthy individuals matched with the study group by gender and age; 2) normal visual acuity examination, intraocular pressure measurement, slit-lamp biomicroscopy, and fundus examination; 3) no other combined ocular, neurological or systemic diseases.

General Information The gender, age, and systemic disease conditions such as hypertension, diabetes, neurological diseases, and similar were recorded for all study subjects. All patients were routinely examined for best-corrected visual acuity (BCVA), intraocular pressure, relative afferent pupillary defect (RAPD), slit-lamp microscopy, visual evoked potential (VEP), visual field, fundus photography, dilated fundus examination, and cranial and orbital MRI. For statistical analysis, BCVA fractional visual acuity was converted to LogMAR, LogMAR = lg (1/fractional visual acuity), for minimum resolution angular logarithmic visual acuity.

OCTA testing OCTA scans were performed by the same skilled ophthalmic professional using the OptovueRTVue XR OCTA machine to obtain OCTA images of a 4.5 mm×4.5 mm area centered on the optic disc, and a 6 mm×6 mm area centered on the fovea region. In order to avoid errors, the scans were repeated three times, and images with a central position and a signal quality index >6 were selected as the images to be analyzed using the Angio Vue software system that came with the device.

Indexes of the optic disc The density of all vessels and capillary were collected for the whole area of optic disc, inside the optic disc, and peripapillary (superior-hemi, inferior-hemi), as well as capillary density for the four subdivisions of the peripapillary region, *i.e.*, temporal, superior, nasal and inferior sides. The whole area of optic disc included the entire 4.5 mm×4.5 mm scanning area of the optic disc; inside the optic disc: a circular area with a 1 mm radius centered on the optic disc; peripapillary: a circular area with a 1-2 mm radius centered on the optic disc, divided into superior-hemi, inferior-hemi and temporal, superior, nasal and inferior subdivisions. The density of all vessels means the percentage of area occupied by large vessels and capillaries within the scanning area; capillary density: the percentage of area occupied by capillaries in the scanned area.

The indexes of the macular The density of superficial capillary plexus (SCP) and the deep capillary plexus (DCP) in the whole area of macular and its subdivisions (superior-hemi, inferior-hemi), the parafovea and perifovea regions, as well as its subdivisions (superior-hemi, inferior-hemi, temporal, superior, nasal, inferior) were collected. The whole area of macular included the entire 6 mm×6 mm scanning area of the macular; parafovea: a circular area with a 0.5-1.5 mm radius centered on the macular fovea; perifovea: a circular area with a 1.5-3.0 mm radius centered on the macular fovea. SCP refers to the area from the internal limiting membranes to 10 μm above the lower edge of the inner plexiform layer, while DCP refers to the area from 10 μm above the lower edge of the inner plexiform layer to 10 μm below the outer plexiform layer.

Statistical Analysis SPSS 26.0 statistical software was used for statistical analysis. The Shapiro-Wilk test was used for measurement data, and data conforming to the normal distribution were expressed as mean±SD; the count data were expressed as percentages. Comparisons between the affected and contralateral eye groups were made using the paired-samples t-test if they had normal distribution and the Wilcoxon signed-rank sum test if they had non-normal distribution. For comparisons between the affected and healthy control groups and between the contralateral and healthy control groups, the independent samples t-test was used if they had normal distribution, and the Mann-Whitney U-test was used if they had non-normal distribution. The Fisher's Exact Test was used for counting data. $P<0.05$ indicated statistically significant differences.

RESULTS

General Information A total of 16 eyes ($n=16$) in the ON-affected eye group and 16 eyes ($n=16$) in the contralateral eye group were finally included in this study. Among those, 8 patients were presented as papillitis and 8 patients were retrobulbar ON. The healthy control group included 20 eyes ($n=20$), there were no significant differences in gender and age between the groups ($P>0.05$). The duration of disease in the affected eyes was distributed from 7 to 90 d, with a mean duration of 32.53±31.90 d. The visual acuity in the affected eyes was significantly reduced compared to the healthy control group, and the difference was statistically significant ($P<0.05$).

Vessel Density in the Optic Disc Area

Comparison between the affected eye group and the contralateral eye group The density of all vessels and capillary were reduced in the whole area of optic disc, and all subdivisions of the peripapillary region in the ON group compared with the uninvolved contralateral eye group ($P<0.05$); there was also no significant difference in the density of capillary vessel inside the optic disc ($t=-2.074$, $P=0.055$; Table 1).

Table 1 Comparison of vessel density in the optic disc between the optic neuritis-affected eye group and the contralateral eye group

($\bar{x}\pm s$, %)

Vessel density	Capillary				All-vessel			
Regions	Affected eye group	Contralateral eye group	t/z	P	Affected eye group	Contralateral eye group	t/z	P
Whole image	44.16±7.15	49.95±3.52	−3.620	0.002	50.52±6.72	56.51±3.54	−4.000	0.001
Inside disc	47.39±7.24	50.16±6.65	−2.074	0.055[b]	56.11±5.32	60.28±4.99	−3.939	0.004
Peripapillary	45.39±8.62	52.85±4.11	−4.032	0.001	53.30 (47.55, 56.25)	59.70 (57.95, 61.25)	−3.621	0.000[a]
Superior hemi	48.40 (41.35, 51.15)	53.40 (51.55, 55.25)	−3.243	0.001[a]	53.30 (47.60, 57.30)	60.00 (58.55, 61.85)	−3.574	0.000[a]
Inferior hemi	45.84±7.71	52.65±4.28	−4.226	0.001	51.45±6.75	58.51±4.24	−4.760	0.000
Temporal	50.00 (39.00, 52.50)	55.00 (52.50, 57.00)	−3.111	0.002[a]				
Superior	48.00 (35.00, 52.00)	55.00 (53.00, 56.50)	−3.627	0.000[a]				
Nasal	44.00 (40.50, 47.00)	48.00 (44.50, 52.00)	−2.804	0.005[a]				
Inferior	48.82±8.15	57.18±4.17	−4.920	0.000				

Paired samples t-test, [a]Wilcoxon signed rank-sum test, [b]$P>0.05$ suggesting a difference that is not statistically significant.

Comparison between the affected eye group and the control group The density of all capillary and vessels were reduced in the whole area of optic disc, and all subdivisions of the peripapillary region in the ON group compared with the healthy control group ($P<0.05$), while no significantly difference were observed inside the optic disc ($t=-0.730$, $P=0.470$; $t=-1.281$, $P=0.209$; Table 2).

Comparison between the contralateral eye group and the control group There was no significant difference in the density of capillary and all vessels in the whole area of optic disc, inside the optic discand all subdivisions of the peripapillary region in the uninvolved contralateral eyes of ON patients compared with the control group (all $P>0.05$; Table 3).

Vessel Density in the Macular

Comparison between the affected eye and the contralateral eye group Compared to the uninvolved contralateral eye group, the density of SCP was significantly lower in the whole area of macular and perifovea region, and its all subdivisions of the ON eye, as well as in the superior-hemi and superior subdivision of the parafovea region (all $P<0.05$). There was no significant difference in the density of DCP between the ON affected eye groupand the uninvolved contralateral eye group (Table 4).

Comparison between the affected eye group and the control group Compared to the control group, the density of SCP in the inferior-hemi, nasal, and inferior perifovea region was significantly reduced in the ON affected eye group ($P<0.05$). There was no significant difference in the density of DCP between the ON affected eye group and the control group ($P>0.05$; Table 5).

Comparison between the contralateral eye group and the control group Compared with the control group, the uninvolved contralateral eye group showed an increase in the density of SCP in the whole area of macular and all its subdivisions ($P<0.05$), as well as an increase in the parafovea area ($P<0.05$); however, the changes in the inferior-hemi and nasal subdivisions were not significantly different ($P>0.05$), and the increase in the density of SCP in the perifovea region was only significant in the superior-hemi and superior subdivisions ($P<0.05$). There was no significant difference in the density of DCP between the contralateral eye group and the control group ($P>0.05$; Table 6).

Table 2 Comparison of vessel density in the optic disc between the affected eye group and the control group in patients with optic neuritis ($\bar{x}\pm s$, %)

Vessel density	Capillary				All-vessel			
Regions	Affected eye group	Healthy control group	t/U	P	Affected eye group	Healthy control group	t/U	P
Whole image	44.16±7.15	50.16±2.65	-3.274	0.004	50.52±6.72	56.04±2.43	-3.214	0.004
Inside disc	47.39±7.24	49.03±6.35	-0.730	0.470[b]	56.11±5.32	58.37±5.35	-1.281	0.209[b]
Peripapillary	45.39±8.62	53.40±3.02	-3.645	0.002	51.29±7.45	59.04±2.98	-4.026	0.001
Superior hemi	44.95±9.82	53.76±3.16	-3.546	0.002	51.09±8.38	59.70±3.04	-4.041	0.001
Inferior hemi	45.84±7.71	53.04±3.13	-3.602	0.002	51.45±6.75	58.33±3.10	-3.866	0.001
Temporal	50 (39, 52.5)	56.5 (55, 58.75)	26.000	0.000[a]				
Superior	43.88±11.12	54.85±4.79	-3.778	0.001				
Nasal	42.94±8.50	47.70±4.01	-2.117	0.046				
Inferior	48.82±8.15	56.20±4.07	-3.390	0.003				

Independent samples t-test, [a]Mann-Whitney U-test, [b]$P>0.05$ suggesting a difference that is not statistically significant.

Table 3 Comparison of vessel density in the optic disc between the contralateral eye group and the control group in patients with optic neuritis ($\bar{x}\pm s$, %)

Vessel density	Capillary				All-vessel			
Regions	Contralateral eye group	Healthy control group	t/U	P	Contralateral eye group	Healthy control group	t/U	P
Whole image	50.70 (48.50, 51.90)	50.45 (48.00, 51.45)	151.500	0.577[a]	57.30 (54.90, 58.55)	56.00 (54.30, 57.30)	126.000	0.187[a]
Inside disc	50.16±6.65	49.03±6.35	0.532	0.598	61.80 (58.40, 62.95)	60.20 (53.33, 63.03)	138.000	0.341[a]
Peripapillary	53.60 (51.50, 55.10)	53.40 (51.37, 55.35)	168.000	0.964[a]	59.70 (57.95, 61.25)	58.70 (56.70, 61.05)	136.500	0.311[a]
Superior hemi	53.40 (51.55, 55.25)	54.10 (51.55, 56.38)	157.500	0.707[a]	60.00 (58.55, 61.85)	59.25 (57.73, 61.45)	147.500	0.497[a]
Inferior hemi	53.40 (51.00, 55.15)	52.75 (51.28, 54.70)	156.500	0.684[a]	59.30 (57.60, 61.25)	57.90 (55.75, 60.98)	134.500	0.283[a]
Temporal	55.00 (52.50, 57.00)	56.50 (55.00, 58.75)	109.000	0.065[a]				
Superior	55.00 (53.00, 56.50)	55.00 (51.50, 58.75)	160.000	0.775[a]				
Nasal	47.94±4.90	47.70±4.01	0.165	0.870				
Inferior	57.18±4.17	56.20±4.07	130.500	0.232				

Independent samples t-test, [a]Mann-Whitney U-test.

Table 4 Comparison of macular vessel density between the affected eye group and the contralateral eye group

($\bar{x}\pm s$,%)

Vessel density	SCP				DCP			
Regions	Affected eye group	Contralateral eye group	t/z	P	Affected eye group	Contralateral eye group	t	P
Whole image	43.95 (36.58, 48.65)	47.95 (45.50, 50.05)	−2.793	0.005[a,b]	44.31±4.69	46.64±3.59	−1.531	0.147
Superior hemi	44.85 (36.80, 49.78)	48.95 (46.15, 51.30)	−2.844	0.004[a,b]	45.42±4.72	47.64±3.37	−1.444	0.169
Inferior hemi	42.27±6.32	46.56±4.29	−2.700	0.016[b]	43.24±4.83	47.45±4.15	−1.568	0.138
Parafovea	45.10 (40.45, 49.90)	50.25 (47.03, 51.25)	−1.836	0.066[a]	51.72±3.66	53.23±3.12	−1.215	0.243
Superior hemi	45.25 (41.63, 50.18)	51.30 (47.68, 52.43)	−2.172	0.030[a,b]	52.18±3.87	54.23±2.74	−1.630	0.124
Inferior hemi	44.52±5.92	47.46±5.59	−1.580	0.135	51.24±3.76	52.24±3.60	−0.773	0.452
Temporal	45.86±6.46	49.12±5.07	−1.551	0.100	54.23±3.34	54.34±2.88	−0.104	0.919
Superior	45.28±6.55	50.34±4.34	−2.726	0.006[b]	50.24±4.73	53.06±3.14	−1.988	0.065
Nasal	44.46±5.02	47.18±5.22	−1.495	0.156	53.77±2.92	55.08±3.52	−1.172	0.259
Inferior	44.23±6.45	47.71±6.76	−1.729	0.104	48.64±5.00	50.40±4.64	−0.970	0.348
Perifovea	44.15 (36.20, 48.95)	48.80 (46.03, 50.23)	−2.844	0.004[a,b]	44.81±5.27	47.68±3.83	−1.653	0.119
Superior hemi	45.05 (36.35, 49.68)	49.65 (46.33, 51.53)	−3.051	0.002[a,b]	45.80±4.81	48.41±3.38	−1.646	0.120
Inferior hemi	42.36±6.78	46.89±4.28	−2.777	0.014[b]	44.45 (38.40, 48.95)	48.60 (41.53, 51.40)	−1.086	0.278[a]
Temporal	40.40±5.20	43.56±3.16	−2.577	0.021[b]	49.02 (45.13, 52.75)	52.45 (48.65, 54.78)	−1.704	0.088[a]
Superior	45.95 (36.20, 50.38)	49.45 (45.15, 52.13)	−3.026	0.002[a,b]	44.47±5.25	46.91±3.56	−1.452	0.167
Nasal	45.24±7.72	50.52±5.43	−2.775	0.014[b]	44.65±6.16	46.91±4.66	−1.070	0.302
Inferior	41.99±7.79	47.63±4.57	−3.056	0.008[b]	41.80 (36.75, 47.75)	47.45 (40.78, 49.98)	−1.086	0.278[a]

Paired samples t-test, [a]Wilcoxon signed rank-sum test; [b]$P<0.05$ suggesting a statistically significant difference. SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

Table 5 Comparison of macular vessel density between the affected eye group and the control group in patients with optic neuritis

($\bar{x}\pm s$, %)

Vessel density	SCP				DCP			
Regions	Affected eye group	Healthy control group	t	P	Affected eye group	Healthy control group	t	P
Whole image	42.86±6.46	45.04±3.10	−1.239	0.229	44.31±4.69	44.86±5.21	−0.328	0.745
Superior hemi	43.44±6.80	45.17±3.42	−0.930	0.363	45.42±4.72	45.68±5.03	−0.159	0.875
Inferior hemi	42.27±6.32	44.91±2.90	−1.546	0.138	43.24±4.83	44.08±5.53	−0.447	0.637
Parafovea	44.96±5.67	46.34±3.88	−0.867	0.392	51.72±3.66	52.14±4.76	−0.292	0.772
Superior hemi	45.38±6.00	46.73±4.48	−0.772	0.445	52.18±3.87	52.67±4.77	−0.336	0.739
Inferior hemi	44.52±5.92	45.95±3.69	−0.845	0.406	51.24±3.76	51.58±4.93	−0.222	0.826
Temporal	45.86±6.46	47.21±3.47	−0.752	0.460	54.23±3.34	53.90±3.93	0.263	0.794
Superior	45.28±6.55	46.67±5.15	−0.716	0.479	50.24±4.73	50.98±5.59	−0.423	0.675
Nasal	44.46±5.02	45.92±4.53	−0.915	0.367	53.77±2.92	53.97±4.45	−0.152	0.880
Inferior	44.23±6.45	45.57±3.95	−0.725	0.475	48.64±5.00	49.66±6.18	−0.533	0.598
Perifovea	42.89±6.81	46.13±3.07	−1.759	0.094	44.81±5.27	45.56±5.96	−0.397	0.694
Superior hemi	43.43±7.03	46.09±3.44	−1.389	0.180	45.80±4.81	46.01±5.53	−0.120	0.905
Inferior hemi	42.36±6.78	46.17±2.91	−2.096	0.049[b]	43.81±5.99	45.10±6.57	−0.605	0.549
Temporal	40.40±5.20	41.87±3.08	−0.999	0.328	47.78±5.73	49.45±5.44	−0.896	0.376
Superior	43.73±7.76	45.71±4.28	−0.915	0.370	44.47±5.25	43.93±6.03	0.285	0.778
Nasal	45.24±7.72	50.10±3.59	−2.327	0.030[b]	44.65±6.16	44.98±6.24	−0.156	0.887
Inferior	41.99±7.79	47.00±3.48	−2.386	0.027[b]	45.62±5.46	43.87±7.55	0.779	0.441

Independent samples t-test, [b]$P<0.05$ suggesting a statistically significant difference. SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

DISCUSSION

ON is one of the most common diseases in neuro-ophthalmology. A study of its post-onset blood perfusion status is important to further the understanding of the pathophysiological process of ON, assess the extent of retinal damage, and assist in the diagnosis and follow-up of ON. Current studies mainly focused on MS-ON and NMO-ON[4-10]. All ON patients included in our study were screened for infections and immune indicators to exclude infections and autoimmune diseases. This study showed that microcirculation was altered in the optic disc and macular region in patients with idiopathic ON.

Table 6 Comparison of macular vessel density between the contralateral eye group and the control group in patients with optic neuritis ($\bar{x}\pm s$, %)

Vessel density	SCP				DCP			
Regions	Contralateral eye group	Healthy control group	t/U	P	Contralateral eye group	Healthy control group	t/U	P
Whole image	47.95 (45.50, 50.05)	44.85 (42.68, 47.00)	84.500	0.015[a,b]	48.40 (44.03, 49.93)	44.65 (41.90, 49.08)	126.500	0.290[a]
Superior hemi	48.95 (46.15, 51.30)	45.60 (42.55, 47.68)	85.500	0.016[a,b]	47.64±3.37	45.68±5.03	1.338	0.190
Inferior hemi	47.55 (44.93, 48.65)	44.75 (43.25, 46.88)	91.000	0.028[a,b]	48.10 (41.38, 49.08)	44.20 (40.65, 48.43)	133.500	0.404[a]
Parafovea	50.25 (47.03, 51.25)	46.80 (43.20, 49.10)	87.500	0.020[a,b]	53.23±3.12	52.14±4.76	0.437	0.437
Superior hemi	51.30 (47.68, 52.43)	47.25 (43.48, 50.15)	90.500	0.026[a,b]	54.23±2.74	52.67±4.77	1.163	0.253
Inferior hemi	49.05 (46.20, 50.00)	46.00 (43.10, 49.13)	102.000	0.067[a]	52.24±3.60	51.58±4.93	0.454	0.653
Temporal	50.80 (47.63, 52.28)	46.90 (44.28, 50.63)	97.000	0.046[a,b]	54.34±2.88	53.90±3.93	0.391	0.699
Superior	50.34±4.34	46.67±5.15	2.279	0.029[b]	53.06±3.14	50.98±5.59	1.329	0.193
Nasal	47.18±5.22	45.92±4.53	0.775	0.443	55.08±3.52	53.97±4.45	0.818	0.419
Inferior	49.80 (48.45, 50.78)	45.10 (43.25, 48.33)	92.000	0.030[a,b]	50.40±4.64	49.66±6.18	0.398	0.693
Perifovea	47.66±4.03	46.13±3.07	99.000	0.053	47.68±3.83	45.56±5.96	1.230	0.227
Superior hemi	49.65 (46.33, 51.53)	46.40 (43.53, 48.50)	92.000	0.030[a,b]	48.41±3.38	46.01±5.53	1.522	0.137
Inferior hemi	48.35 (45.63, 49.20)	45.90 (44.58, 48.05)	114.000	0.149[a]	48.60 (41.53, 51.40)	45.35 (41.10, 50.55)	138.000	0.498[a]
Temporal	43.90 (41.63, 46.10)	41.60 (40.53, 42.75)	100.500	0.058[a]	51.41±3.99	49.45±5.44	1.205	0.237
Superior	48.75±4.32	45.71±4.28	2.109	0.042[b]	46.91±3.56	43.93±6.03	109.500	0.109
Nasal	52.05 (48.23, 53.88)	50.40 (46.85, 52.75)	131.500	0.369[a]	46.91±4.66	44.98±6.24	1.028	0.311
Inferior	49.35 (45.40, 50.30)	46.75 (44.43, 49.25)	122.500	0.236[a]	45.62±5.46	43.87±7.55	0.779	0.441

Independent samples t-test, [a]Mann-Whitney U test; [b]$P<0.05$ suggesting a statistically significant difference. SCP: Superficial capillary plexus; DCP: Deep capillary plexus.

In the present study, we collected the density of all vessels in the optic disc area, as well as the capillary density after the removal of large vessels, finding that the density of all vessels and capillary of the peripapillary region were reduced in the ON eye group compared to the uninvolved contralateral eye group and healthy control group. Fard *et al*[12] and Rougier *et al*[13] used OCTA to analyze the density of the peripapillary region in ON patients with acute optic nerve head edema and found it was reduced, which is consistent with the results of the present study, and suggests that microcirculation in the optic disc region is already impaired at ≤3 mo. The results of several previous studies have shown that patients with MS-ON and NMO-ON with an ON lasting >6 mo had reduced vessel density of the peripapillary region compared to their uninvolved contralateral eyes and healthy control eyes[7,9-11,14-15]. However, there are few studies on OCTA in acute phase ON and a lack of comparative studies of vessel density in the acute and chronic phases. Therefore, further refinement of the follow-up time is needed to observe and explore the changes during the disease progression. At the same time, although vessel density inside the optic disc of the eyes with ON decreased compared to the healthy control group and the uninvolved contralateral eye group, the difference was not statistically significant. Therefore, we speculated that vessel density of the peripapillary and inside the optic disc region might be differently affected during the pathological process of idiopathic ON. In the present study, the density of capillary and all vessels in the optic disc area were not significantly altered in the uninvolved contralateral eyes of patients with ON lasting for ≤3 mo compared to healthy control eyes, whereas in several previous studies, patients with MS-ON or NMO-ON lasting for >6 mo, vessel density in the optic disc area was decreased in uninvolved contralateral eyes compared to the healthy control group[7,9-10,16]. Presumably, this is due to a chronic process of altered microcirculation in the contralateral eyes[11]. However, these studies did not exclude the effect of primary lesions on retinal blood perfusion, thus, future studies are needed for further verification.

Although our study and the study by Fard *et al*[12] and Rougier *et al*[13] found a decrease in vessel density in the optic disc region at ≤3 months of ON disease, the measurement of optic disc vessel density in the affected eyes may be subject to error due to earlyoptic disc swelling. Also, vessel density in the macular, which is less affected by optic disc swelling, has recently received increasing attention from neuro-ophthalmologists. In our study, the density of SCP in the inferior-hemi and inferior perifovea region was significantly reduced in the ON affected eye group, and the same decrease in SCP density in the parafovea region compared to the healthy control group was also found in the study by Lee *et al*[11] and Yu *et al*[17] suggesting that in addition to the damage to the microcirculation in the optic disc area, blood perfusion in the macular region was also affected during ON disease. It is currently believed that the causes of reduced retinal blood perfusion include primary vascular dysfunction and reduced metabolic demand due to optic atrophy. According to the first view, vascular dysfunction is primarily associated with optic inflammation or demyelinating diseases. The second view suggests that a reduction in neurons and axons leads to

reduced metabolic activity in the inner layers of the retina, which subsequently leads to a reduction in oxygen and blood demand, eventually resulting in superficial vascular degeneration[6,17]. In the present study, the SCP density in the parafovea region did not significantly change compared to the healthy control group. However, Lee *et al*[11] and Yu *et al*[17] reported that patients' SCP density in the parafovea region significantly decreased compared to the healthy control group when the duration of ON disease was >6 and 3 mo, respectively, so it is presumed that the early SCP damage caused by ON in the macular region may have spread from the peri-macular region to the center. As they did not analyze the vessel density in the perifovea region, it is not possible to make further comparisons, so further longitudinal studies are needed to confirm the reported data. The present study showed that DCP density did not significantly differ between the ON-affected eye group, uninvolved contralateral, and control groups. The DVP blood flow density was reduced in the affected eyes of ON patients with a disease duration of >6 mo compared to the healthy control group[6,9,18], which was presumably due to a reduction in neurons and axons resulting in reduced metabolic activity in the inner retinal layers and degeneration of the superficial vessels, subsequently affecting the deep retinal vessels supplied by the superficial vascular anastomoses[6,17]. Further follow-up observations are required. Our findings showed that the SCP density in some subdivisions of the perifovea region was reduced in eyes with ON compared to the healthy control group, whereas the SCP density in the superior-hemi subdivision of the parafovea and perifovea region were all increased in the contralateral eye group compared to the healthy control group. This phenomenon remains unclear, however, it is speculated that there may be a compensatory increase in SCP density in the macular region of the contralateral eye in the early phase of ON. Due to a lack of studies on the contralateral eye in the early stages of ON, future studies are needed for further confirmation. Therefore, a partitioned analysis of SCP and DCP in the ON-affected eye and the uninvolved contralateral eye in the early stages of ON is necessary to further explore and elucidate its pathogenesis. In summary, our findings suggest that patients with ON in the duration of < 3 mo may showed a decreased vessel density in all peripapillary subdivisions, and a decreased density of SCP in some subdivisions of the perifovea region, accompanied by an increased density of SCP in some subdivisions of the macular region of the contralateral eyes. As the sample size was too small to allow for subgroup analysis by etiology, we plan to expand the sample size in our future study to analyze and compare the changes in retinal blood perfusion between ON subgroups with different etiologies. Long-term follow-up is also needed to observe changes in vessel density in ON patients during disease progression.

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