



Carotid disease and retinal optical coherence tomography angiography parameters in patients with non-arteritic anterior ischemic optic neuropathy

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Abstract

Purpose In order to analyze the data and retinal microvasculature for non-arteritic anterior ischemic optic neuropathy (NAION), patients were referred to have carotid Doppler ultrasound (CDU) from 2016 to 2020.

Methods In this case–control observational study, 30 NAION patients were evaluated with CDU. Twenty-two NAION patients (at least 3 months after the onset of symptoms) and 9 normal subjects underwent a complete ophthalmic examination including optical coherence tomography (OCT) and optical coherence tomography angiography (OCT-A). NAION eyes and fellow eyes were further divided into two groups based on the presence of carotid stenosis (CS). NAION patients with CS were termed “CS-NAION”; and those without CS were termed “NCS-NAION.” Measurements of radial peripapillary capillary vessel density (RPC VD), ganglion cell complex (GCC), retinal nerve fiber layer (RNFL) thicknesses were compared among groups.

Results Fourteen of 30 NAION patients referred to have carotid Doppler were positive for CS with each one of such referrals having less than 50% stenosis. RNLF, GCC and RPC VDs were reduced in NAION

patients’ eyes, when compared to controls and the fellow eyes. RPC VD was significantly lower in the temporal-superior ($P = 0.037$) and the superior-temporal ($P = 0.012$) sectors of the NCS-NAION patients than in the CS-NAION patients. No significant differences were found between CS-fellow eyes and NCS-fellow eyes in terms of RPC VDs, RNLF or GCC.

Conclusion Results of the study highlight the effect of the carotid artery stenosis on ocular perfusion pressure in the pathogenesis of NAION. More extensive studies are necessary.

Keywords Non-arteritic anterior ischemic optic neuropathy · Optical coherence tomography angiography · Carotid artery stenosis · Peripapillary capillary density

Introduction

Acute optic nerve injury due to non-arteritic anterior ischemic optic neuropathy (NAION) typically causes reduced visual acuity and significant retinal structural alterations, which is almost always permanent. In recent years, imaging method such as optical coherence tomography has been used extensively to document any swelling and injury at the various retinal layers [1–3]. Given the claimed ischemic

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pathophysiology, fluorescein angiography (FA) and optic coherence angiography (OCT-A) imaging techniques have explored the blood flow or the vasculature in the region of the optic nerve head (ONH), peripapillary retina and choroid. Fluorescein and indocyanine green angiographic studies of the optic disk in NAION showed complete or sectorial delay or absence of filling of the prelaminar optic disk without impairment of the choroidal circulation [4, 5]. However, FA is not sufficiently sensitive enough to measure the detailed changes of capillaries. OCT-A is a noninvasive technique that provides analysis of the microvasculature of the peripapillary region. Previous studies have reported that the swelling of the ONH in NAION causes significant changes in the peripapillary vasculature both at the acute and the atrophic stage [6–10]. As previously described, OCT-A findings show very good matching with retinal nerve fiber layer (RNFL) and visual field damages, confirmed by correlation analyses [8, 10].

The risk factors for the development of the NAION are hypertension, arteriosclerosis, diabetes, cardiovascular disease and internal carotid artery occlusion [11, 12]. Color-flow Doppler is a new development of duplex sonography of the peripheral vessels. In a retrospective study with duplex sonography, authors evaluated 191 ophthalmological patients with amaurosis fugax, occluded retinal veins and glaucoma, and found that ophthalmological patients suffered more often from carotid artery stenosis (CS) than asymptomatic people [13].

Given that the carotid artery disease can contribute to development of NAION either by embolism or by lowering the perfusion pressure [12], the aim of this study is to evaluate the effect of CS on the capillary density within the optic disk and within the peripapillary region in NAION eyes and the fellow eyes.

Methods

This observational cross-sectional study was conducted in Bakırköy Dr. Sadi Konuk Education and Research Hospital which is located in Istanbul, Turkey. Patients with NAION were recruited from the neuroophthalmology clinic. The research protocols were approved by the institutional review board, and it adhered to the tenets of the Declaration of

Helsinki. Written informed consent was obtained from all volunteers prior to their participation in this study.

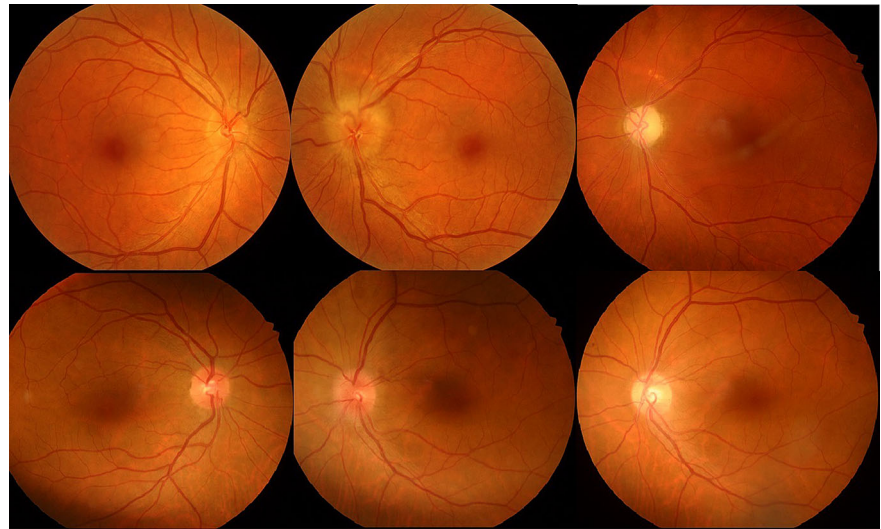
Diagnostic criteria for NAION were: a sudden onset of painless vision loss, sectorial or generalized optic disk edema, peripapillary hemorrhage and normal erythrocyte sedimentation rate or C-reactive protein. All of the patients underwent ophthalmic evaluation, including best-corrected visual acuity (BCVA) and refraction assessments, slit-lamp biomicroscopy, intraocular pressure measurement, ONH evaluation, fundus examination and digital color fundus photography (digital non-mydratic retinal camera; Topcon), carotid color Doppler sonography (CDU). Representative cases of NAION are shown in Fig. 1. Twenty-two NAION patients in the atrophic phase were retrospectively identified from an internally maintained OCT-A imaging database (at least 3 months of the initial evaluation). OCT-A images of fellow, unaffected eyes were also evaluated in the study. NAION patients were categorized as either NAION with CS “CS-NAION” or NAION without CS “NCS-NAION” based on the presence or absence of CS, at the CDU.

The control group comprised age-matched subjects with a BCVA \geq 0,8, IOP \leq 21 mm Hg, an open angle, normal optic disk appearance on fundus examination and no RNFL defects.

The exclusion criteria were as follows: (1) refractive error greater than + 3.0 diopters (D) or less than – 4.0 D; (2) previous intraocular surgery other than cataract; (3) any other ophthalmic disorder, including corneal opacity, vitreous opacity, diabetic retinopathy and diseases affecting the optic disk such as glaucoma, optic neuritis, uveitis, retinal or choroidal diseases, and trauma; and (4) neurologic diseases that may affect the optic nerve such as multiple sclerosis, Alzheimer disease and Parkinson disease (5) poor cooperation in OCT imaging studies.

OCT-A was performed with the spectral domain system RTVue-XR Avanti (Optovue Inc. Fremont, California, USA). The peripapillary RNFL was determined using the ONH protocol. A standard 360°, 3.4-mm-diameter circular scan was utilized to measure the RNFL thickness, and the superior, nasal, temporal and inferior RNFL values were recorded. The macula cube scanning protocol measured the ganglion cell complex (GCC) thickness over a 7 mm diameter centered on the fovea, inferior, superior and the total GCC values were recorded.

Fig. 1 First row: Color fundus photography of NAION patient without carotid artery stenosis, fellow eye and the NAION eye in the atrophic stage. Second row: Color fundus photography of NAION patient with carotid artery stenosis, fellow eye and the NAION eye in the atrophic stage



The flow density map software AngioAnalytics (RTVue-XR version 2018.0.0.18) was employed to quantify the vessel density in this study. The OCT-A images were acquired within the peripapillary area (Fig. 2). The retinal peripapillary capillaries (RPC) mode, which included the signals from the internal limiting membrane to the nerve fiber layer, was utilized in this study. In the optic disk scan, the software automatically fits an ellipse to the optic disk margin and calculates the average vessel density within the ONH and peripapillary area. The peripapillary area is defined as a 0.75-mm-wide elliptical annulus that extends from the optic disk boundary. The peripapillary region is divided into sectors, and the vessel densities in each sector are calculated. The sectors are: nasal-inferior, nasal-superior, inferonasal, inferotemporal, superotemporal, superonasal, temporal-inferior and temporal-superior sectors. The vessel density (VD) was defined as the percentage of the area that is occupied by vessels within the segmented area. The signal strength index was employed to control the image quality. Images with a signal strength index less than 7 were excluded.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) 26.0 version (IBM Corporation, New York, USA). The mean, standard deviation, maximum, minimum, frequency and ratio values were used as appropriate in the descriptive summary of the data. Normal distribution of the variables was assessed by the Kolmogorov–Smirnov test. The Mann–Whitney U test and the

Kruskal–Wallis test were used for the comparison of quantitative data. A p value less than 0.05 was considered statistically significant.

Results

This study was designed to analyze data for NAION patients referred to have CDU from 2016 to 2020. Thirty NAION patients were evaluated with CDU in the present study. There were 14 patients with CS in the NAION group. Eight patients had contralateral CS, five patients had bilateral CS, and one patient had ipsilateral CS. The degree of stenosis was below the 50% mark in all fourteen patients.

Twenty-two of the 30 atrophic NAION patients and 9 controls were analyzed with OCT-A in the study. Nine of the 22 NAION patients (6 men and 3 women, age 60.3 ± 8.7 years) had CS; there was no CS in 13 NAION patients (6 men and 7 women, age 55.0 ± 8.5 years). Patients were aged 59.82 ± 8.2 years (5 men and 4 women) in control group. Two patients with CS and three patients without CS had bilateral NAION. The mean BCVA (decimal) was 0.55 ± 0.30 in the CS-NAION patients, 0.45 ± 0.36 in the NCS-NAION patients and one in the control subjects. Of the 22 patients with NAION, 10 eyes from 9 NAION patients with CS and 16 eyes from 13 NAION patients without CS were imaged in the atrophic phase. Seventeen unaffected (fellow) eyes were also analyzed by OCT-A using the same

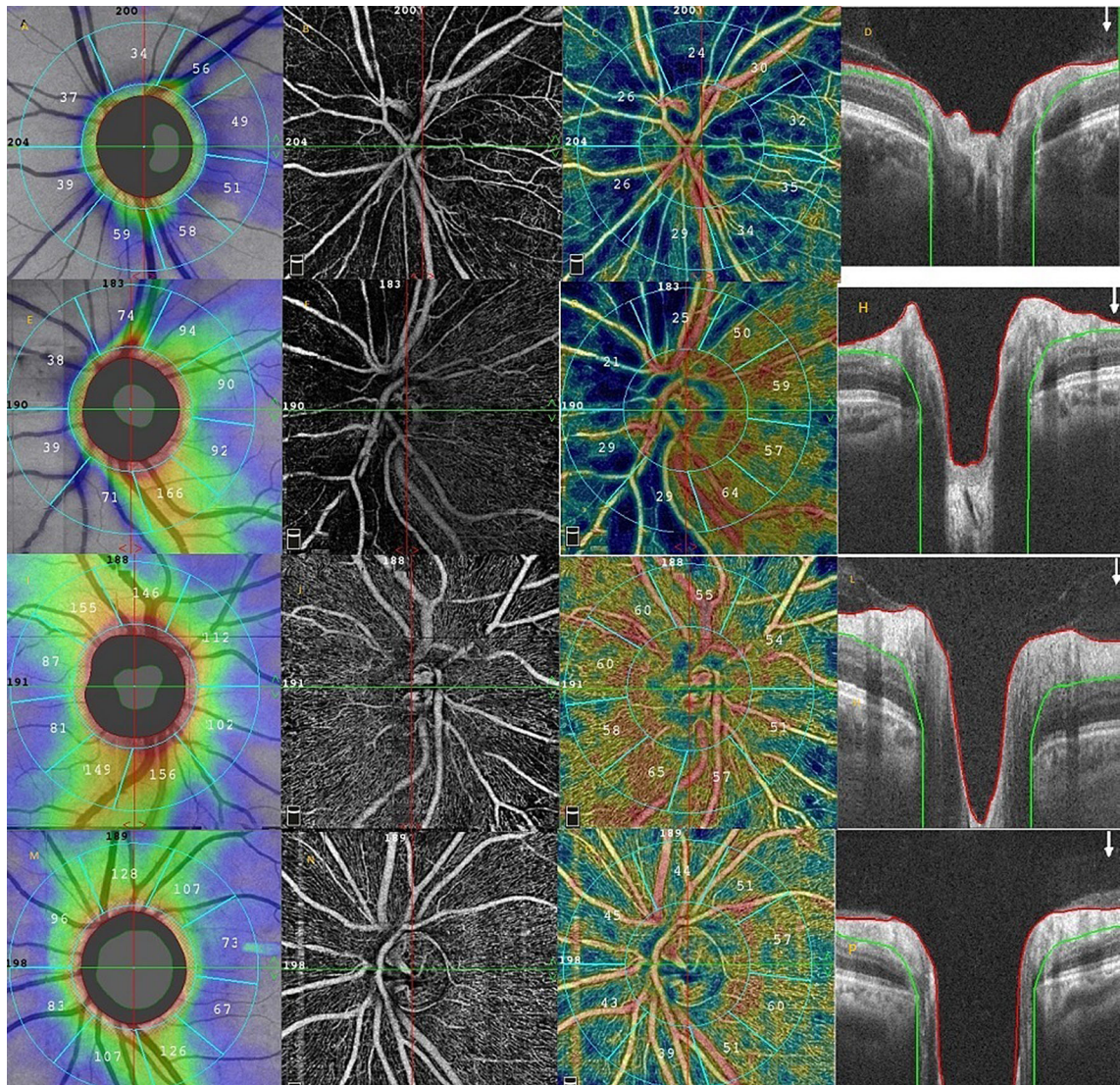


Fig. 2 OCT-A images of the subjects; first row: NAION patient without carotid stenosis, second row: NAION patient with carotid stenosis, third row: fellow eye of NAION patient with carotid stenosis, last row: healthy control. First two cases showed a damage of retinal nerve fiber layer (RNLF) (A, E) which was more extensive in the NAION patient without carotid stenosis (A). Diffuse (A) and sectorial vascular perfusion defect

(E) in en face optical coherence tomography angiograms in the radial peripapillary capillary (RPC) layer consistent with the blue areas on color vascular density map. OCT-A reveals a normal vascular network in the fellow eye of the NAION patient with carotid artery stenosis (J, K) and healthy control (N, O). Last column, B-scan image of the segmentation of the optic nerve head radial peripapillary capillary plexus of the subjects

quantitative method for comparison between the eyes with CS (n:7) and without CS (n:10). All 7 fellow eyes of CS-NAION patients had ipsilateral CS.

The mean GCC thickness parameters (μm) and RNLF thickness parameters (μm) were comparable between the CS-NAION, NCS-NAION patients and significantly lower in both of the groups than in the

healthy controls. The quantitative results are presented in Table 1.

Table 1 shows the retinal peripapillary capillaries vessel density (RPC VD) (%) results for the peripapillary area in CS-NAION, NCS-NAION and control groups. The RPC VDs were significantly lower in all the sectors of the peripapillary area in both of the

Table 1 Demographics, ganglion cell complex thickness (GCC), peripapillary retinal nerve fiber layer (RNLF) thickness and vessel density (VD) in healthy eyes, NAION eyes with carotid artery stenosis and NAION eyes without carotid artery stenosis: univariate and multivariate analysis

	A Mean ± sd	B Mean ± sd	C Mean ± sd	P value	P ^{AC}	P ^{BC}	P ^{AB}
Age	60.3 ± 8.7	55.0 ± 8.5	59.1 ± 8.2	0.483	0.699	0.470	0.200
Visual acuity	0.55 ± 0.30	0.45 ± 0.36	1.00 ± 0.00	0.000	0.000	0.000	0.558
GCC-average (µm)	77.9 ± 14.1	69.9 ± 9.9	95.9 ± 5.1	0.000	0.003	0.000	0.215
GCC-superior (µm)	72.4 ± 15.4	66.6 ± 9.9	95.6 ± 6.1	0.000	0.000	0.000	0.235
GCC-inferior (µm)	83.5 ± 20.0	73.4 ± 14.5	96.6 ± 4.9	0.001	0.048	0.000	0.205
RNFL-superior (µm)	81.2 ± 25.5	59.9 ± 24.2	120.4 ± 12.2	0.000	0.000	0.000	0.052
RNFL-nasal (µm)	76.3 ± 37.5	68.8 ± 18.9	96.3 ± 10.3	0.000	0.039	0.000	0.833
RNFL-inferior (µm)	90.3 ± 30.0	90.8 ± 46.5	130.7 ± 12.0	0.001	0.002	0.003	0.598
RNFL-temporal (µm)	54.7 ± 16.7	53.1 ± 14.0	70.9 ± 11.7	0.000	0.008	0.000	0.895
c/d Volume ratio	0.04 ± 0.14	0.19 ± 0.26	0.26 ± 0.29	0.072	0.053	0.306	0.105
c/d Area ratio	0.02 ± 0.06	0.08 ± 0.12	0.14 ± 0.18	0.069	0.052	0.262	0.121
Disk area (mm ²)	2.03 ± 0.28	2.17 ± 0.47	1.99 ± 0.43	0.522	0.669	0.377	0.280
Whole VD (%)	40.2 ± 4.1	36.6 ± 6.5	47.7 ± 1.6	0.000	0.000	0.000	0.146
Inside VD (%)	47.8 ± 4.0	43.6 ± 7.0	46.9 ± 4.5	0.088	0.649	0.080	0.050
Peripapillary VD (%)	40.4 ± 6.4	35.2 ± 6.9	49.9 ± 2.6	0.000	0.000	0.000	0.091
Superior-hemi VD (%)	38.5 ± 7.1	32.9 ± 6.4	50.0 ± 2.3	0.000	0.000	0.000	0.081
Inferior-hemi VD (%)	42.4 ± 7.2	37.6 ± 8.6	52.6 ± 13.1	0.000	0.004	0.000	0.170
Nasal-superior VD (%)	33.3 ± 13.9	33.9 ± 8.6	47.2 ± 4.2	0.000	0.002	0.000	0.912
Nasal-inferior VD (%)	38.9 ± 8.6	35.8 ± 9.2	45.8 ± 3.2	0.002	0.036	0.000	0.359
Inferior-nasal VD (%)	42.8 ± 13.0	33.9 ± 10.0	47.8 ± 6.8	0.004	0.378	0.000	0.169
Inferior-temporal VD (%)	47.9 ± 13.2	39.5 ± 14.8	54.5 ± 3.9	0.033	0.392	0.012	0.113
Temporal-inferior VD (%)	40.2 ± 10.5	40.7 ± 10.3	50.9 ± 4.7	0.006	0.014	0.004	0.874
Temporal-superior VD (%)	43.4 ± 7.3	36.9 ± 8.4	53.5 ± 5.5	0.000	0.002	0.000	0.037
Superior-temporal VD (%)	40.1 ± 10.0	29.4 ± 8.4	54.4 ± 2.6	0.000	0.000	0.000	0.012
Superior-nasal VD (%)	34.6 ± 10.4	29.2 ± 8.4	46.9 ± 4.2	0.000	0.003	0.000	0.119

Kruskal Wallis/Mann–Whitney U test

Values are presented as the mean ± standard deviation

Statistically significant values are shown in bold

A: NAION eyes with carotid artery stenosis

B: NAION eyes without carotid artery stenosis

C: Healthy controls

P^{AC}: Difference with control eyes & NAION eyes with carotid artery stenosis

P^{BC}: Difference with control eyes & NAION eyes without carotid artery stenosis

P^{AB}: Difference with NAION eyes without carotid stenosis & NAION eyes with carotid artery stenosis

groups than in the healthy controls. This density was significantly lower in the temporal-superior ($P = 0.037$) and the superior-temporal ($P = 0.012$) sectors of the NCS-NAION patients than in the CS-NAION patients.

The mean GCC thickness (µm), RNLF thickness (µm) and RPC VD (%) results for the fellow eyes of the NAION patients are shown in Table 2. All of the measurements were comparable between the groups except for the visual acuity ($P = 0.001$ for both) (Table 2).

Table 2 Demographics, ganglion cell complex thickness (GCC), peripapillary retinal nerve fiber layer (RNLF) thickness and vessel density (VD) in healthy eyes, fellow eyes with carotid artery stenosis and fellow eyes without carotid artery stenosis: univariate and multivariate analysis

	D Mean ± sd	E Mean ± sd	F Mean ± sd	P value	p ^{DF}	p ^{EF}	p ^{DE}
Age	63.8 ± 12.0	56.2 ± 12.8	59.1 ± 8.2	0.423	0.423	0.768	0.410
Visual acuity	0.86 ± 0.16	0.92 ± 0.18	1.00 ± 0.00	0.001	0.001	0.040	0.230
GCC-average (μm)	93.1 ± 22.2	94.7 ± 13.6	95.9 ± 5.1	0.339	0.339	0.763	0.845
GCC-superior (μm)	91.9 ± 22.6	93.1 ± 15.9	95.6 ± 6.1	0.408	0.408	0.633	1.000
GCC-inferior (μm)	94.3 ± 22.4	96.6 ± 12.0	96.6 ± 4.9	0.426	0.426	0.960	0.845
RNFL-superior (μm)	103.0 ± 44.9	121.0 ± 28.4	120.4 ± 12.2	0.726	0.726	0.406	0.328
RNFL-nasal (μm)	89.0 ± 41.2	103.0 ± 31.5	96.3 ± 10.3	0.357	0.357	0.940	0.435
RNFL-Inferior (μm)	102.7 ± 34.3	129.1 ± 28.7	130.7 ± 12.0	0.052	0.052	0.841	0.130
RNFL-temporal (μm)	65.1 ± 22.0	73.5 ± 17.9	70.9 ± 11.7	0.726	0.726	0.598	0.464
c/d volume ratio	0.07 ± 0.19	0.08 ± 0.16	0.26 ± 0.29	0.082	0.082	0.080	0.883
c/d area ratio	0.03 ± 0.08	0.02 ± 0.05	0.14 ± 0.18	0.082	0.082	0.080	0.883
Disk area (mm ²)	1.96 ± 0.32	2.04 ± 0.44	1.99 ± 0.43	0.924	0.924	0.581	0.625
Whole VD (%)	46.3 ± 9.3	47.3 ± 3.3	47.7 ± 1.6	0.386	0.386	0.819	0.556
Inside VD (%)	49.6 ± 4.8	49.9 ± 5.2	46.9 ± 4.5	0.126	0.126	0.137	0.845
Peripapillary VD (%)	47.4 ± 11.4	49.6 ± 3.7	49.9 ± 2.6	0.544	0.544	0.839	0.731
Superior-hemi VD (%)	45.7 ± 13.9	49.4 ± 4.1	50.0 ± 2.3	0.501	0.501	0.704	0.806
Inferior-hemi VD (%)	48.7 ± 9.1	49.5 ± 3.3	52.6 ± 13.1	0.924	0.924	0.723	0.659
Nasal-superior VD (%)	43.7 ± 12.6	47.3 ± 5.1	47.2 ± 4.2	0.798	0.798	0.980	0.922
Nasal-inferior VD (%)	44.3 ± 9.8	44.2 ± 4.9	45.8 ± 3.2	0.949	0.949	0.349	0.659
Inferior-nasal VD (%)	48.9 ± 10.3	50.2 ± 5.7	47.8 ± 6.8	0.656	0.656	0.327	1.000
Inferior-Temporal VD (%)	55.4 ± 8.0	55.7 ± 2.3	54.5 ± 3.9	0.503	0.503	0.507	0.588
Temporal-inferior VD (%)	47.6 ± 10.1	50.0 ± 4.7	50.9 ± 4.7	0.482	0.482	0.464	0.769
Temporal-superior VD (%)	48.4 ± 14.7	50.2 ± 5.2	53.5 ± 5.5	0.924	0.924	0.113	0.405
Superior-temporal VD (%)	48.6 ± 16.3	51.9 ± 7.6	54.4 ± 2.6	0.369	0.369	0.578	0.769
Superior-nasal VD (%)	43.4 ± 14.1	47.4 ± 5.4	46.9 ± 4.2	0.874	0.874	0.840	0.961

Kruskal Wallis/Mann–Whitney U test

Values are presented as the mean ± standard deviation

Statistically significant values are shown in bold

D: Fellow eyes of NAION patients with carotid artery stenosis

E: Fellow eyes of NAION patients without carotid artery stenosis

F: Healthy controls

p^{DF}: Difference with control eyes & fellow eyes of NAION patients with carotid artery stenosis

p^{EF}: Difference with control eyes & fellow eyes of NAION patients without carotid artery stenosis

p^{ED}: Difference with fellow eyes of NAION patients with carotid artery stenosis & fellow eyes of NAION patients without carotid artery stenosis

Fellow eyes and NAION eyes of both categories of patients showed similar disk area and cup to disk ratio, cup to disk volume ratio parameters as in healthy controls. The quantitative results are presented in Tables 1 and 2.

Discussion

The optic disk blood flow in NAION was previously investigated using various methods. Using a laser Doppler flowmeter, Leiba et al. demonstrated that the

ONH blood flow in NAION eyes is significantly lower than that in healthy control eyes [14]. A decrease in peripapillary retinal perfusion has also been reported in NAION eyes by using Doppler OCT [15]. OCT-A is currently the preferred method for mapping ocular perfusion, including capillaries. Recently, several studies on ocular microvasculature in NAION have been reported. Some studies have examined NAION eyes with swollen disks using OCT-A, and reported the dilation of patent superficial capillaries in the peripapillary area [16] and the reduction of the peripapillary vascular density associated with the acute phase of NAION [6, 7]. Some other studies have also assessed microvascular changes in atrophic NAION eyes using OCT-A [8, 10, 17]. Liuet al. studied 13 eyes of 13 NAION patients and reported the quantitative OCT-A results for non-acute NAION eyes [9]. Similar to the present study, they found a reduced vascular density in peripapillary area. Two quantitative studies, also using Optovue devices, reported microvascular attenuation in the non-acute phase of NAION with correlation between the areas of vascular attenuation and RNFL atrophy or visual field loss [8, 10]. The authors proposed that the decreased RNFL and GCC owing to NAION results in decreased metabolic activities and blood flow via auto-regulatory mechanisms [8, 10, 17]. Of interest, the current study, which evaluated 22 patients with NAION and a control group, to the best of knowledge, is the first to investigate the association between NAION and carotid disease using the OCT-A derived vessel density measurements. In the present study, the eyes of the NAION patients were analyzed in subgroups based on the presence of CS, and contralateral unaffected eyes were included, in order to analyze the eventual possible differences with respect to healthy controls. This study confirmed the statistically significant vascular impairment occurring in NAION eyes, and there was a difference between the VD parameters in the sub-group analysis. VD showed significant reductions in superior-temporal region in NCS-NAION when compared to the CS-NAION patients. Previously, Yu et al. reported significantly smaller diameter RPCs in the temporal region [18]. Accordingly, it can be speculated that due to the capillaries with smaller diameters, the hemodynamic instabilities might affect the temporal sectors selectively. In the current study, all fellow eyes of the patients had ipsilateral CS. However, the fellow and

normal eyes showed no significant difference in vessel density at the peripapillary region among the groups. These results indicate that the VD may not be affected in CS. It is worth noting that the degree of obstruction was below the 50% in all of the fellow eyes. However, the sample size was small to draw an accurate conclusion and more research is needed in the future, to confirm these findings as well as to determine the results in larger groups.

Keeping in mind that the human eye is an embryological protrusion of the brain and that the optic nerve is a tract of the brain, neuroimaging has been widely used to exclude neoplastic and other nervous system diseases affecting visual function and optic nerve. Magnetic resonance imaging and diffusion weighted magnetic resonance imaging have been widely employed for the evaluation of the optic nerve's involvement of orbital disease and tumors [19–21]. The internal carotid artery supplies blood to the eye; therefore, the stenosis of the carotid artery caused by atherosclerosis may affect its visual functioning. A video fluorescein angiography study on 33 patients with carotid artery stenosis by Wolf et al. reported decreased retinal perfusion in all patients and prolonged arteriovenous passage of time in 18 of them [22]. Investigative modalities like CDU and computed tomography angiography (CTA) have been studied in the diagnosis of CS [23, 24]. CTA uses ionizing radiation and requires contrast agent administration. CDU is a cost effective, noninvasive and safe imaging modality that allows the operator to assess the caliber of the carotid arteries in addition to the blood flow and velocities. Operator variability is one of the biggest weaknesses of CDU as an imaging modality. The sensitivity and specificity of both imaging modalities decrease in low-grade CS [24].

The pathogenesis of acute NAION is believed to be multifactorial, including the acute hypo-perfusion of short posterior ciliary arteries [12, 25, 26] There has been no thrombosis demonstrated in the short posterior ciliary arteries in the histopathological studies performed in NAION eyes [27, 28]. This hypo-perfusion depends on several factors including variations in blood pressure, increase of intraocular pressure, local vasculopathy and impairment in blood flow autoregulation [12, 26]. There is a complex vascular supply to the eye. Kaup et al. compared the retrobulbar hemodynamics of patients with acute NAION with healthy age-matched controls and reported that the ophthalmic

artery showed no differences in hemodynamics between patients with NAION and controls [29]. In the present study, 14 of the 30 NAION patients had carotid artery stenosis. In carotid artery disease, the association of NAION has been studied previously. Hayreh et al. evaluated a cohort of 266 eyes with NAION and found a 51% prevalence of carotid artery plaques in the involved side [30]. Zhu et al. demonstrated that the presence of carotid artery plaque was more frequent in the patients with NAION, compared to either the hypertensive group or the normal controls, indicating that NAION may be associated with carotid artery atherosclerosis [31]. Although it was found that the carotid disease was more often in NAION patients, the mechanism is unclear. Zhu et al. suggested that the association might be due to similar pathological changes of the inner vascular walls in the carotid artery and the arteries supplying the optic nerve head. Carotid artery stenosis results in decrease of blood pressure in the ocular vascular bed, and the severity of blood flow reduction depends upon the degree of stenosis. In carotid artery disease, hemodynamic disturbances can also be produced by other mechanisms. One possible explanation might be the disruption of vasomotor autoregulation. It has been showed that the serotonin released by platelets aggregation on atherosclerotic plaques in the carotid artery may trigger transient vasospastic occlusion [32]. Recently, Mense et al. demonstrated that patients with CS had impaired baroreceptor reflex and reduced cerebral autoregulation, which could lead to hemodynamic insufficiency [33]. It is not known why the sensitivity of baroreceptors in the carotid sinus is impaired in patients with CS. Previously Kitagawa proposed that the thickness and rigidity of carotid atheromatous plaque could impede the transmission of intraluminal pressure to the adventitia where baroreceptors exist [34].

Given that the CS was at the contralateral side in most of the NAION patients, this result was unexpected. Based on the findings of the current study, it can be suggested that the CS might activate the compensatory mechanisms to avoid the reduction of the ocular blood flow on the ipsilateral side in chronic situations. These mechanisms might be protective against the serious perfusion reduction which could be responsible for an irreversible vascular damage. However, this hypothesis requires further studies to be proved.

The study had several limitations. One of the main drawbacks was the small study population. This is a cross-sectional study with a single observation at one specific point, and therefore, larger scale prospective longitudinal studies with the implementation of both OCT-A and carotid imaging must be conducted to obtain data that are more reliable. Additionally, vasculature in different layers was not evaluated due to the limits of the current technology. Finally, here, this study focused on carotid disease, yet retro-orbital circulation was not analyzed.

In conclusion, this study showed normal VD of the clinically normal fellow eyes in the presence of CS in NAION. Further prospective studies with a large number of patients are warranted to elucidate the associations between carotid disease and NAION and to investigate the pathophysiology of NAION. Larger prospective longitudinal studies will need to be conducted in order to clarify the long-term effect of CS on ocular vasculature.

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