Carotid Disease and Retinal Optical Coherence Tomography Angiography Parameters in Patients with Non-arteritic Anterior Ischemic Optic Neuropathy

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Research Article

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Abstract

Purpose: To analyze the data and retinal microvasculature for nonarteritic anterior ischemic optic neuropathy (NAION) patients referred to have carotid Doppler ultrasound from 2016 to 2020.

Methods: In this case-control observational study, 30 NAION patients evaluated with carotid doppler sonography. 22 NAION patients (at least 3 months after onset of symptoms) and 9 normal subjects underwent a complete ophthalmic examination including optical coherence tomography (OCT), optical coherence tomography angiography (OCT-A). NAION eyes and fellow eyes were further divided into the groups according to presence of carotid stenosis (CS). NAION patients with CS were termed "CS-NAION"; those without were termed "NCS-NAION". Measurements of radial peripapillary capillary vessel density (RPC VD) and ganglion cell complex (GCC), disk retinal nerve fiber layer (RNFL) thickness were compared among groups.

Results: Fourteen of 30 NAION patients referred for carotid Doppler were positive for CS with all of such referrals having less than 50% stenosis. RNFL, GCC and RPC VDs were reduced in NAION 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, RNFL or GCC.

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

Introduction

Acute optic nerve injury due to nonarteritic anterior ischemic optic neuropathy (NAION) typically causes reduced visual acuity (VA) and significant retinal structural alterations, which almost always is permanent. In recent years imaging methods, such as optical coherence tomography has been used extensively to document swelling and injury at the various retinal layers [1, 2, 3]. Given the claimed ischemic pathophysiology, florescein 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 disc in NAION showed complete or sectorial delay or absence of filling of the prelaminar optic disc without impairment of the choroidal circulation [4, 5]. However, FA is not sufficiently sensitive to measure the detailed changes of capillaries. OCT-A is a non-invasive technique that provides analysis of the microvasculature of the peripapillary region. Previous studies have reported that swelling of the ONH in NAION causes significant changes in the peripapillary vasculature both at the acute and the atrophic stage [6, 7, 8, 9, 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 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
disc and within the peripapillary region in NAION and the fellow eyes.

Methods

This observational cross-sectional study was conducted in Bakırköy Dr. Sadi Konuk Education and Research Hospital (Istanbul, Turkey). Patients with NAION were recruited from neuroophthalmology clinic.

The research protocols were approved by the institutional review board and 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 disc 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-Mydriatic Retinal Camera; Topcon), carotid colour doppler sonography.

Representative cases of NAION are shown in Fig. 1. Twenty-two patients 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 carotid colour doppler sonography.

The control group comprised age-matched subjects with a BCVA ≥ 0.8, IOP ≤ 21 mm Hg, an open angle, normal optic disc appearance on fundus examination, and no RNFL defects.

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 disc (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 superior, nasal, temporal and inferior RNFL values were recorded. The macula cube scanning protocol measured the ganglion cell complex (GCC) thickness over a 7mm diameter centered on the fovea, inferior, superior and total GCC values were recorded.

The flow density map software AngioAnalytics (RTVue XR version 2018.0.0.18) was automatically employed to quantify 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 internal limiting membrane to the nerve fiber layer was employed in this study. In the optic disc scan, the software automatically fits an ellipse to the optic disc 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 disc boundary. The peripapillary region is divided into sectors, and the vessel densities in each sector are calculated (nasalinferior, nasalsuperior, inferonasal, inferotemporal, superotemporal, superonasal, temporalinferior and temporalsuperior sectors). For each scanned region, the software automatically calculates the vessel densities. The vessel density (VD) was defined as the percentage of the area occupied by vessels within the segmented area. The signal strength index was employed
to control for image quality. Images with a signal strength index less than 7 were excluded, and scans with movement or decentration artifacts were repeated.

Results

This study was designed to analyse data for NAION patients referred to have carotid Doppler ultrasound from 2016 to 2020. Thirty NAION patients evaluated with carotid doppler sonography in the present study. There were 14 patients with CS in the NAION group. Eight patients had contralateral CS, 5 patients bilateral CS and 1 patient had ipsilateral CS. The degree of stenosis was below the 50% in all patients.

Twenty two of the 30 NAION patients and 9 controls were analyzed with OCTA 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 3 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 1 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 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, RNFL thickness parameters 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
Demographics, Ganglion Cell Complex Thickness, Peripapillary Retinal Nerve Fiber Layer Thickness and Vessel Density in Healthy eyes, NAION eyes with Carotid Artery Stenosis and NAION eyes without Carotid Artery Stenosis: Univariate and Multivariate Analysis

|                | A               | B               | C               | \(P_{\text{value}}\) | \(P^{\text{AC}}\) | \(P^{\text{BC}}\) | \(P^{\text{AB}}\) |
|----------------|-----------------|-----------------|-----------------|------------------------|-------------------|-------------------|-------------------|
| 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    | 77,9 ± 14,1     | 69,9 ± 9,9      | 95,9 ± 5,1      | 0,000                  | 0,003             | 0,000             | 0,215             |
| GCC-Superior   | 72,4 ± 15,4     | 66,6 ± 9,9      | 95,6 ± 6,1      | 0,000                  | 0,000             | 0,000             | 0,235             |
| GCC-Inferior   | 83,5 ± 20,0     | 73,4 ± 14,5     | 96,6 ± 4,9      | 0,001                  | 0,048             | 0,000             | 0,205             |
| RNFL-Superior  | 81,2 ± 25,5     | 59,9 ± 24,2     | 120,4 ± 12,2    | 0,000                  | 0,000             | 0,000             | 0,052             |
| RNFL-Nasal     | 76,3 ± 37,5     | 68,8 ± 18,9     | 96,3 ± 10,3     | 0,000                  | 0,039             | 0,000             | 0,833             |
| RNFL-Inferior  | 90,3 ± 30,0     | 90,8 ± 46,5     | 130,7 ± 12,0    | 0,001                  | 0,002             | 0,003             | 0,598             |
| RNFL-Temporal  | 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             |
| Disc Area      | 2,03 ± 0,28     | 2,17 ± 0,47     | 1,99 ± 0,43     | 0,522                  | 0,669             | 0,377             | 0,280             |
| Whole          | 40,2 ± 4,1      | 36,6 ± 6,5      | 47,7 ± 1,6      | 0,000                  | 0,000             | 0,000             | 0,146             |
| Inside         | 47,8 ± 4,0      | 43,6 ± 7,0      | 46,9 ± 4,5      | 0,088                  | 0,649             | 0,080             | 0,050             |
| Peripapillary  | 40,4 ± 6,4      | 35,2 ± 6,9      | 49,9 ± 2,6      | 0,000                  | 0,000             | 0,000             | 0,091             |
| Superior-Hemi  | 38,5 ± 7,1      | 32,9 ± 6,4      | 50,0 ± 2,3      | 0,000                  | 0,000             | 0,000             | 0,081             |

Kruskal Wallis / Mann-Whitney U test

Values are presented as the mean ± standard deviation.

Systatically significant values are shown in bold.

A: NAION Eyes with Carotid Artery Stenosis
B: NAION Eyes without Carotid Artery Stenosis
C: Healthy Controls

\(P^{\text{AC}}\) : Difference with Control eyes & NAION Eyes with Carotid Artery Stenosis

\(P^{\text{BC}}\) : Difference with Control eyes & NAION Eyes without Carotid Artery Stenosis

\(P^{\text{AB}}\) : NAION Eyes without Carotid Stenosis & NAION Eyes with Carotid Artery Stenosis
|                    | A                | B                | C                | P value | pAC   | pBC   | pAB   |
|--------------------|------------------|------------------|------------------|---------|-------|-------|-------|
|                    | Mean ± sd        | Mean ± sd        | Mean ± sd        |         |       |       |       |
| Inferior-Hemi      | 42.4 ± 7.2       | 37.6 ± 8.6       | 52.6 ± 13.1      | 0.000   | 0.004 | 0.000 | 0.170 |
| Nasal-Superior     | 33.3 ± 13.9      | 33.9 ± 8.6       | 47.2 ± 4.2       | 0.000   | 0.002 | 0.000 | 0.912 |
| Nasal-Inferior     | 38.9 ± 8.6       | 35.8 ± 9.2       | 45.8 ± 3.2       | 0.002   | 0.036 | 0.000 | 0.359 |
| Inferior-Nasal     | 42.8 ± 13.0      | 33.9 ± 10.0      | 47.8 ± 6.8       | 0.004   | 0.378 | 0.000 | 0.169 |
| Inferior-Temporal  | 47.9 ± 13.2      | 39.5 ± 14.8      | 54.5 ± 3.9       | 0.033   | 0.392 | 0.012 | 0.113 |
| Temporal-Inferior  | 40.2 ± 10.5      | 40.7 ± 10.3      | 50.9 ± 4.7       | 0.006   | 0.014 | 0.004 | 0.874 |
| Temporal-Superior  | 43.4 ± 7.3       | 36.9 ± 8.4       | 53.5 ± 5.5       | 0.000   | 0.002 | 0.000 | 0.037 |
| Superior-Temporal  | 40.1 ± 10.0      | 29.4 ± 8.4       | 54.4 ± 2.6       | 0.000   | 0.000 | 0.000 | 0.012 |
| Superior-Nasal     | 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

PAC: Difference with Control eyes & NAION Eyes with Carotid Artery Stenosis

PBC: Difference with Control eyes & NAION Eyes without Carotid Artery Stenosis

PAB: NAION Eyes without Carotid Stenosis & NAION Eyes with Carotid Artery Stenosis

Table 1 shows the 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 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 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, Peripapillary Retinal Nerve Fiber Layer Thickness and Vessel Density in Healthy eyes, Fellow eyes with Carotid Artery Stenosis and Fellow eyes without Carotid Artery Stenosis: Univariate and Multivariate Analysis

|                | D: Fellow Eyes of NAION Patients with Carotid Artery Stenosis | E: Fellow Eyes of NAION Patients without Carotid Artery Stenosis | F: Healthy Controls | P-value | pDF | pEF | pDE |
|----------------|---------------------------------------------------------------|---------------------------------------------------------------|--------------------|---------|-----|-----|-----|
|                | Mean ± sd                                                     | Mean ± sd                                                     | Mean ± sd         |         |     |     |     |
| 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 | 0.263 |
| GCC-Average    | 93.1 ± 22.2                                                   | 94.7 ± 13.6                                                   | 95.9 ± 5.1        | 0.339   | 0.339 | 0.763 | 0.845 |
| GCC-Superior   | 91.9 ± 22.6                                                   | 93.1 ± 15.9                                                   | 95.6 ± 6.1        | 0.408   | 0.408 | 0.633 | 1.000 |
| GCC-Inferior   | 94.3 ± 22.4                                                   | 96.6 ± 12.0                                                   | 96.6 ± 4.9        | 0.426   | 0.426 | 0.960 | 0.845 |
| RNFL-Superior  | 103.0 ± 44.9                                                  | 121.0 ± 28.4                                                  | 120.4 ± 12.2      | 0.726   | 0.726 | 0.406 | 0.328 |
| RNFL-Nasal     | 89.0 ± 41.2                                                   | 103.0 ± 31.5                                                  | 96.3 ± 10.3       | 0.357   | 0.357 | 0.940 | 0.435 |
| RNFL-Inferior  | 102.7 ± 34.3                                                  | 129.1 ± 28.7                                                  | 130.7 ± 12.0      | 0.052   | 0.052 | 0.841 | 0.130 |
| RNFL-Temporal  | 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 |
| Disc Area      | 1.96 ± 0.32                                                   | 2.04 ± 0.44                                                   | 1.99 ± 0.43       | 0.924   | 0.924 | 0.581 | 0.625 |
| Whole          | 46.3 ± 9.3                                                    | 47.3 ± 3.3                                                   | 47.7 ± 1.6        | 0.386   | 0.386 | 0.819 | 0.556 |

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

pDF: Difference with Control eyes & Fellow Eyes of NAION Patients with Carotid Artery Stenosis

pEF: Difference with Control eyes & Fellow Eyes of NAION Patients without Carotid Artery Stenosis

pED: Fellow Eyes of NAION Patients with Carotid Artery Stenosis & Fellow Eyes of NAION Patients without Carotid Artery Stenosis
|       | D: Fellow Eyes of NAION Pateints with Carotid Artery Stenosis | E: Fellow Eyes of NAION Pateints without Carotid Artery Stenosis | F: Healthy Controls | P value | pDF | pEF | pDE |
|-------|-------------------------------------------------------------|-----------------------------------------------------------------|--------------------|---------|-----|-----|-----|
| Inside| **49.6 ± 4.8**                                              | **49.9 ± 5.2**                                                  | **46.9 ± 4.5**     | 0.126   | 0.126 | 0.137 | 0.845 |
|      |                                                            |                                                                 |                    |         |     |     |     |
| Peripapillary | **47.4 ± 11.4**                                          | **49.6 ± 3.7**                                                  | **49.9 ± 2.6**     | 0.544   | 0.544 | 0.839 | 0.731 |
| Superior-Hemi | **45.7 ± 13.9**                                          | **49.4 ± 4.1**                                                  | **50.0 ± 2.3**     | 0.501   | 0.501 | 0.704 | 0.806 |
| Inferior-Hemi  | **48.7 ± 9.1**                                           | **49.5 ± 3.3**                                                  | **52.6 ± 13.1**    | 0.924   | 0.924 | 0.723 | 0.659 |
| Nasal-Superior | **43.7 ± 12.6**                                          | **47.3 ± 5.1**                                                  | **47.2 ± 4.2**     | 0.798   | 0.798 | 0.980 | 0.922 |
| Nasal-Inferior | **44.3 ± 9.8**                                           | **44.2 ± 4.9**                                                  | **45.8 ± 3.2**     | 0.949   | 0.949 | 0.349 | 0.659 |
| Inferior-Nasal | **48.9 ± 10.3**                                          | **50.2 ± 5.7**                                                  | **47.8 ± 6.8**     | 0.656   | 0.656 | 0.327 | 1.000 |
| Inferior-Temporal | **55.4 ± 8.0**                                         | **55.7 ± 2.3**                                                  | **54.5 ± 3.9**     | 0.503   | 0.503 | 0.507 | 0.588 |
| Temporal-Inferior | **47.6 ± 10.1**                                         | **50.0 ± 4.7**                                                  | **50.9 ± 4.7**     | 0.482   | 0.482 | 0.464 | 0.769 |
| Temporal-Superior | **48.4 ± 14.7**                                        | **50.2 ± 5.2**                                                  | **53.5 ± 5.5**     | 0.924   | 0.924 | 0.113 | 0.405 |
| Superior-Temporal | **48.6 ± 16.3**                                        | **51.9 ± 7.6**                                                  | **54.4 ± 2.6**     | 0.369   | 0.369 | 0.578 | 0.769 |
| Superior-Nasal  | **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.

Signstatistically significant values are shown in bold.

D: Fellow Eyes of NAION Pateints with Carotid Artery Stenosis
E: Fellow Eyes of NAION Pateints without Carotid Artery Stenosis
F: Healthy Controls

**pDF**: Difference with Control eyes & Fellow Eyes of NAION Pateints with Carotid Artery Stenosis

**pEF**: Difference with Control eyes & Fellow Eyes of NAION Pateints without Carotid Artery Stenosis

**pDE**: Fellow Eyes of NAION Pateints with Carotid Artery Stenosis & Fellow Eyes of NAION Pateints without Carotid Artery Stenosis

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

In this retrospective study, 14 of the 30 NAION patients had carotid artery stenosis. There was also statistically significant difference in RPC layer between the subgroups of NAION patients in the superior temporal sectors.

The optic disc 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]. 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 discs using OCT-A, and reported dilation of patent superficial capillaries in the peripapillary area (16) and 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, 9, 10]. Liu et 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 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 autoregulatory mechanisms [8, 10, 17]. Results of the current study are in line with the above studies. In the present study, eyes of the NAION patients were analyzed in subgroups according to presence of CS and contralateral unaffected eyes were included, in order to analyze eventual possible differences with respect to healthy controls. This study confirmed the statistically significant vascular impairment occurring in NAION eyes. Fellow eyes of both categories of patients showed normal vascular network similar to healthy controls. In the present study, there was a difference between vessel density parameters in the sub-group analysis. Vessel density showed significant reductions in superior temporal region in NCS-NAION compared to 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 diameter the hemodynamic instabilities might effect temporal sectors selectively.

NAION is presumed to be caused by acute hemodynamic insufficiency in optic nerve circulation, resulting in ONH infarction. The pathogenesis of acute NAION is believed to be multifactorial, including the acute hypoperfusion of short posterior ciliary arteries [12, 19, 20] There has been no thrombosis demonstrated in the short posterior ciliary arteries in the histopathological studies performed in NAION eyes [21, 22]. Internal carotid artery supply blood to the eye, therefore stenosis of internal carotid artery caused by artherosclerosis may effect the 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 arterio-venous passage time in 18 of them[23]. In the current study all fellow eyes of the patients had ipsilateral CS in the CS-NAION group. However, fellow and normal eyes showed no significant difference in vessel density at the paripapillary region among the groups. These results indicate that the capillary vasculature may not be affected in CS. It is worth noting that the degree of obstruction was below the %50 percent in all eyes.

Zhu et al demonstrated that presence of carotid artery plaque was more frequent in the patients with NAION, compared to either the hypertensive group or the normal controls, indicating NAION may be associated with carotid artery atherosclerosis [24]. Their suggestion is in line with our conclusion. Although they found that the CS was more often in NAION patients the mechanism is unclear. One possible explanation might be the disruption of vazomotor autoregulation. Mense et al demonstrated that patients with carotid stenosis had impaired baroreceptor
reflex and reduced cerebral autoregulation which could lead to hemodynamic insufficiency [25]. It is not known why the sensitivity of baroreceptors in the carotid sinus is impaired in patients with carotid stenosis. Previously Kitagawa proposed that thickness and rigidity of carotid atheromatous plaque could impede the transmission of intraluminal pressure to the adventitia where baroreceptors exist [26]. Given that the CS was at the contralateral side in most of the NAION patients this result was unexpected. Based on 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 might be responsible also of an irreversible vascular damage. However, this hypothesis requires further studies to prove.

The study had several limitations. One of the main drawbacks was the small study population. Future research is needed to confirm our findings and also to determine the results in larger groups. This was a cross sectional study with a single observation at one specific point. Further investigation needs to be carried out to clarify the long-term effect of CS on ocular vasculature.

**Declarations**

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Figures

Figure 1

First row: Color fundus photography of NAION patient without carotid stenosis, fellow eye and the NAION eye in the atrophic stage. Second row: Color fundus photography of NAION patient with carotid stenosis, fellow eye and the NAION eye in the atrophic stage.
Figure 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 (OCT-A) in the radial peripapillary capillary (RPC) layer consistent with the blue areas on color vascular density map. OCT-angiography reveals a normal vascular network in the fellow eye of the NAION patient with carotid 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.