

# Evaluation of Optical Coherence Tomography Angiography Changes in Non-arteritic Anterior Ischemic Optic Neuropathy

## Non-arteritik Anterior İskemik Optik Nöropatide Optik Koherens Tomografi Anjiyografi Değişikliklerinin Değerlendirilmesi

Delil Özcan<sup>1</sup>, Murat Karapapak<sup>2</sup>, Dilber Çelik Yaprak<sup>3</sup>

<sup>1</sup>University of Health Sciences Türkiye, Seyrantepe Hamidiye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

<sup>2</sup>University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

<sup>3</sup>University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

### ABSTRACT

**Background:** To explore microvascular changes in the optic disc (OD) of eyes with non-acute non-arteritic anterior ischemic optic neuropathy (NAION) using optical coherence tomography angiography (OCTA).

**Materials and Methods:** This cross-sectional study enrolled patients with NAION for a duration exceeding 3 months along with healthy volunteers. Vascular density (VD) measurements for OD were obtained across the entire area, inside the disc peripapillary, and in the superior and inferior hemi-regions using OCTA on a 4.5 mm scan.

**Results:** The mean age of the 41 NAION patients and 47 volunteers in the healthy group was 64.8±7.9 years and 62.9±7.5 years, respectively. No significant differences were observed in the sex and age distribution between the NAION patients and the healthy group. The mean VD of the optic nerve in the whole image for NAION patient eyes, fellow eyes, and the healthy group were 47.4±2.1, 50.0±2.3, and 49.6±2.0, respectively. Notably, the entire image VD in the NAION group was significantly lower than that in the other groups (p=0.001). Peripapillary and inferior VD in eyes with NAION were significantly lower than those in the other groups. However, no significant differences were observed in the inside disc and superior hemi VD between the patient and fellow eyes of NAION patients and the healthy group (p>0.179, p>0.829, respectively).

**Conclusion:** This study demonstrated a significant reduction in entire image, peripapillary, and superior hemi VD of the OD in NAION patients during the chronic period.

**Keywords:** Non-arteritic anterior ischemic optic neuropathy, optic disc, optical coherence tomography angiography, vascular density

### ÖZ

**Amaç:** Non-arteritik anterior iskemik optik nöropatili (NAION) gözlerde optik diskteki (OD) mikrovasküler değişiklikleri optik koherens tomografi anjiyografi (OKTA) ile incelemektir.

**Gereç ve Yöntemler:** Bu kesitsel çalışmaya 3 aydan uzun süreli NAION hastaları ve sağlıklı kontrol grubu gönüllüleri dahil edilmiştir. OD'nin (4,5x4,5 mm) tüm alan, disk içi, peripapiller, süperior yarı ve inferior yarı vasküler dansitesi (VD) OKTA kullanılarak elde edilmiştir.

**Bulgular:** Çalışmaya dahil edilen 41 NAION hastasının ve 47 kontrol grubu gönüllülerinin sırasıyla yaş ortalaması 64,8±7,9 yıl ve 62,9±7,5 yıldır. NAION hastaları ve kontrol grubunun cinsiyet ve yaş dağılımları arasında anlamlı farklılık izlenmemiştir. NAION hastalarının hasta gözlerinde optik sinirin ortalama tüm alan VD'si, diğer gözlerinin ve kontrol grubunun VD'si sırasıyla 47,4±2,1, 50,0±2,3 ve 49,6±2,0 idi ve NAION grubunda tüm alan VD diğer gruplardan istatistiksel olarak anlamlı derecede düşüktü (p=0,001). NAION izlenen gözlerde peripapiller ve inferior VD diğer gruplardan anlamlı olarak düşüktü. NAION hastalarının hasta ve diğer gözü ile kontrol grubu arasında diskiçi ve süperior yarı VD arasında anlamlı farklılık izlenmemiştir (sırasıyla p>0,179, p>0,829).

**Sonuç:** Bu çalışma, kronik dönemde NAION hastalarında OD'nin tüm alan, peripapiller ve süperior yarı VD'nin önemli ölçüde azaldığını göstermektedir.

**Anahtar Kelimeler:** Non-arteritik anterior iskemik optik nöropati, optik disk, optik koherens tomografi anjiyografi, vasküler dansite



**Address for Correspondence:** Murat Karapapak, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

Phone: +90 545 214 12 03 E-mail: mrtkarapapak@gmail.com ORCID ID: orcid.org/0000-0001-9604-6887

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## Introduction

The most prevalent acute optics neuropathy in individuals aged 50 years and above is non-arteritic anterior ischemic optics neuropathy (NAION) (1). The primary pathology underlying NAION is vascular insufficiency in the optic nerve, which stems from decreased hydrostatic pressure in the posterior ciliary arteries (2). It is presumed to be associated with vascular insufficiency due to the loss of autoregulation. Despite the involvement of an interconnected series of factors, the pathophysiology of NAION remains not fully understood. The optic disc (OD) in these patients is typically small and crowded, potentially exacerbating blood flow jeopardy and leading to compartment syndrome.

Clinically, NAION typically manifests as a painless, sudden loss of monocular vision accompanied by a relative afferent pupillary defect, visual field loss, and OD edema, with or without nerve fiber thickening around the OD (3). Optic nerve damage can result in severe visual impairment or blindness. Early diagnosis is crucial for prompt and effective management of the disease. However, there is still no gold standard method for NAION diagnosis, necessitating a comprehensive diagnosis based on typical clinical symptoms, fundus findings, visual fields, and fundus fluorescein angiography (FFA) changes in the clinical setting.

Optical coherence tomography angiography (OCTA) is a novel vascular imaging technology that can rapidly and non-invasively visualize the vascular morphology and vessel density (VD) around the OD and macular area without the need for injectable dye or enhanced capillary imaging features (4,5). It can also perform qualitative analysis of retinal and choroidal vasculature disorders along with optic neuropathy. Several studies have previously used OCTA to identify microvascular changes in NAION (6,7). These studies have shown that acute and chronic NAION patients with OD edema have decreased peripapillary VD and a relationship between the superotemporal region and NAION. However, it is important to note that there is limited information about the ability of OCTA to diagnose eyes with NAION.

This study aimed to retrospectively evaluate the clinical data of patients in the chronic phase of NAION, focusing on OCTA features.

## Materials and Methods

Between May 2018 and November 2021, 41 eyes diagnosed with chronic phase NAION and 41 fellow eyes of 41 patients in the outpatient clinic of our hospital were included in the study. In addition, 47 randomly selected eyes

of 47 healthy individuals without any ocular or systemic disease were included. The diagnostic criteria for NAION were established based on previously defined criteria (8): 1) absence of ocular and systemic diseases that may affect or explain the patient's visual problems and sudden decrease in visual acuity; 2) visual field defects associated with OD pathologies; 3) regional or diffuse OD edema and peripapillary hemorrhage; 4) presence of relative afferent pupillary defects and/or impaired visual evoked potentials; 5) exclusion of other OD diseases. In the NAION group, all patients were consulted by the neurology department. Best corrected visual acuity assessment, anterior and posterior segment examinations with slit lamp microscopy, intraocular pressure measurement with applanation method, color fundus photography, visual field tests, and visual evoked potential examinations were performed in all patients. Only patients without contraindications underwent FFA. The study adhered to the principles of the Helsinki Declaration, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 3255, date: 27/04/2021).

The inclusion criteria encompassed patients with NAION who had passed a 3-month period since the disease onset and were not in the acute phase. The exclusion criteria were as follows: 1) patients with non-NAION or acute-phase NAION; 2) non-acute phase NAION patients with concurrent eye pathologies; 3) inadequate cooperation or weak fixation for OCTA assessment; 4) ODs with abnormal anatomy hindering OCTA evaluation; and 5) individuals with a spherical equivalent refractive error exceeding  $\pm 5.0$  diopters (D) or astigmatism greater than  $\pm 3.0$  D. The control group comprised healthy individuals with normal ODs and no systemic or ocular diseases.

## Optical Coherence Tomography Angiography Imaging

OD images, measuring 4.5 mm, were captured using OCTA with AngioVue Avanti RTVue-XR software, version 2017 (OptoVue, Fremont, CA, USA). VD in the whole area, within the disc and in the peripapillary regions of OD were meticulously examined. Image segmentation was performed using the RTVue software without manual adjustments. The device's algorithm autonomously analyzed the OD and peripapillary region, dividing it into several vascular layers. The software then automatically calculated the average VD for entire OD image, inside the disc peripapillary, superior hemi, and inferior hemi. Following the definition of the OD boundaries, the VD measurement is executed by analyzing the layer extending from the internal limiting membrane to 150  $\mu\text{m}$  within this membrane for the OD. Radial peripapillary VD analysis was then conducted from the



internal limiting membrane on the retinal nerve fiber layer for measuring superficial peripapillary VD. To ensure data quality, ten images with a low signal strength index (<70) from 51 symptomatic eyes of patients with NAION were excluded. This exclusion criteria considered factors such as motion artifacts, blinking, and low image quality.

### Statistical Analysis

Descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency, and ratio values, were employed to characterize the data. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For the analysis of quantitative independent data, Mann-Whitney U and Kruskal-Wallis tests were used. The Wilcoxon test was applied to analyze dependent quantitative data, whereas the chi-square test was employed for the analysis of qualitative independent data. All statistical analyses were performed using SPSS version 28.0.

### Results

Among the NAION patients, there were 17 females (41.4%) and 24 males (58.6%), whereas the healthy group comprised 19 females (40.4%) and 28 males (59.6%). The mean ages of NAION patients and the healthy group were 64.8±7.9 years and 62.9±7.5 years, respectively. Demographic and clinical data for both the NAION patients and the healthy group are summarized in Table 1. Notably, there were no significant differences in gender and age distributions between the NAION patients and the healthy group (p>0.05). In the eyes of patients with NAION disease, fellow eyes, and eyes in the healthy group, the logMAR values were 1.05±0.21, -1.06±0.35, and -1.03±1.58, respectively (p<0.001). In addition, there were no significant differences in axial length and cup/disc ratio between the NAION patients and the healthy group (p>0.05). Smokers were observed as follows: in the NAION group, 11 out of 41 patients (26.8%); and in the healthy

control group, 13 out of 47 volunteers (27.6%). Statistical analysis revealed no significant differences in smoking between these groups (p>0.05). In the NAION group, nine patients were on antihypertensive medication for systemic hypertension and three patients were on statin therapy. No history of systemic medication was reported in the healthy control group.

OCTA scans were meticulously analyzed to discern numerical variations in VDs of the OD between NAION patients and the healthy group (Table 2). VD measurements encompassed the whole image, inside the disc peripapillary, superior hemi, and inferior hemi for all eyes in the study. The average VD of the whole image in the affected eyes of NAION patients was significantly lower than that in their fellow eyes and the healthy group (p=0.01). Interestingly, no significant difference was observed in disc VD when comparing the affected eyes of NAION patients, their fellow eyes, and the healthy group. Notably, the peripapillary average VD values for the affected eyes, fellow eyes, and healthy group of NAION patients were 49.8±2.5%, 52.0±2.4%, and 52.7±2.6%, respectively (p=0.000).

Moreover, the average VD in the inferior hemi of affected eyes in NAION patients was significantly lower than that in their fellow eyes and the healthy group (p=0.00). In contrast, the average VD in the superior hemi for affected eyes, fellow eyes, and the healthy group of patients with NAION were 51.1±2.7%, 51.8±5.2%, and 52.9±2.6%, respectively (p>0.05). Importantly, no significant differences were observed between the healthy group and the fellow eyes of patients with NAION concerning the mean VD across the whole image, inside the disc, peripapillary, superior hemi, and inferior hemi.

### Discussion

NAION, a leading cause of sudden vision decline in the elderly, is one of the most prevalent contributors to acute OD ischemia (9). Its etiology is attributed to circulatory

**Table 1. Demographic and clinical characteristics of the participants**

		NAION eye	Fellow eye	Control group	
<b>Age</b>		64.8±7.9/66 (48-74)	64.8±7.9/66 (48-74)	62.9±7.5/65.5 (51-79)	0.448 <sup>a</sup>
<b>Sex</b>	Female	17 (41.4)	17 (41.4)	19 (40.4)	0.317 <sup>b</sup>
	Male	24 (58.6)	24 (58.6)	28 (59.6)	
<b>Lens status</b>	Phakic	23 (56.0)	23 (56.0)	25 (53.1)	0.658 <sup>c</sup>
	Pseudophakic	17 (44.0)	17 (44.0)	22 (46.9)	
<b>Axial length (mm)</b>		23.3±1.5/23.5 (22.4-26.8)	23.2±1.4/23.5 (21.9-27.4)	23±1.5/23.4 (20.1-25.4)	0.411 <sup>a</sup>
<b>Vertical cup/disc ratio</b>		0.41±0.2/1 (0.3-0.7)	0.43±0.2/1 (0.2-0.8)	0.39±0.1/1 (0.2-0.8)	0.945 <sup>a</sup>
<b>Visual acuity (LogMAR)</b>		1.05±0.21/1.2 (0.5-2.0)	-1.06±0.35/0.35/1.3 (1.33)	-1.03±1.58/1.58/1 (1.30.2)	<0.001 <sup>a</sup>

<sup>a</sup>: Mann-Whitney U, <sup>b</sup>: Chi-square test, <sup>c</sup>: Fisher's Exact test, \*: p<0.05, continuous variables are presented as mean ± standard deviation/median (min-max). Categorical variables are presented as number (%), NAION: Non-arteritic anterior ischemic optic neuropathy

**Table 2. Mean vascular densities of the optic disc of patients with NAION and control group**

	Control group		NAION eye		pm	Fellow eye		pm	p*
	Avg. ± SD	Median	Avg. ± SD	Median		Avg. ± SD	Median		
<b>Optic disc (% VD)</b>									
Whole image	50.0±2.3	50.1	47.4±2.1	47.8	<b>0.001<sup>m</sup></b>	49.6±2.0	49.9	0.233 <sup>m</sup>	<b>0.001<sup>w</sup></b>
Inside disc	50.2±5.4	49.7	49.2±4.2	48.7	0.177 <sup>m</sup>	49.8±4.6	49.9	0.352 <sup>m</sup>	0.179 <sup>w</sup>
Peripapillary	52.7±2.6	52.6	49.8±2.5	50.4	<b>0.000<sup>m</sup></b>	52.0±2.4	52.2	0.169 <sup>m</sup>	<b>0.000<sup>w</sup></b>
Superior hemi	52.9±2.6	52.9	51.1±2.7	51.8	0.227 <sup>m</sup>	51.8±5.2	52.6	0.229 <sup>m</sup>	0.829 <sup>w</sup>
Inferior hemi	52.4±3.0	52.7	48.4±2.5	49.5	<b>0.000<sup>m</sup></b>	51.7±2.6	51.2	0.124 <sup>m</sup>	<b>0.000<sup>w</sup></b>

<sup>m</sup>: Mann-Whitney U test, <sup>w</sup>: Wilcoxon test, p: Difference with control group/p, \*: Difference between patient and fellow eye of NAION patients, Avg.: Average, SD: Standard deviation, VD: Vascular density, NAION: Non-arteritic anterior ischemic optic neuropathy

insufficiency in the OD, with anatomical and mechanical factors influencing the risk of NAION development (10). Specifically, a smaller OD with a short radius and a reduced scleral canal are associated with this condition. The increased concentration of nerve fibers within this narrow channel, coupled with the slowing of axoplasmic flow related to OD edema, are considered to be key factors contributing to anterior OD ischemia (11,12). Factors such as vascular insufficiency and hemodynamic alterations are believed to contribute to the development of NAION. The occlusion of short posterior ciliary arteries is specifically associated with NAION development (13). FFA plays a pivotal role in the examination of NAION, revealing early-stage OD hypoperfusion and late-stage dye leakage. However, fluorescein-induced dye leakage can hinder the selection of the vascular network on the OD surface (14). Although FFA provides valuable data on the superficial capillary network of the OD, its capability to visualize deeper vascular structures is limited.

OCTA facilitates the visualization of retinal and peripapillary vessels, allowing the assessment of the superficial vascular plexus within the retinal nerve fiber layer. This is achieved through the detection of motion contrast originating from blood flow, coupled with automatic segmentation provided by its algorithm. Notably, OCTA distinguishes itself from FFA by enabling imaging and evaluation of radial peripapillary capillaries. These capillary connections exhibit a radial distribution around the OD, extending along the nerve fibers and serving as the primary capillary source for radial peripapillary nerve fibers (15). OCTA proves invaluable in the clinical assessment of patients with NAION, offering both structural and vascular measurements of the OD and macula. This capability positions OCTA as a promising biomarker for predicting visual outcomes (16,17). Moreover, the expanding use of OCTA as a non-invasive technology is notable in the evaluation of various optic neuropathies, including conditions such as glaucoma, and in the identification of underlying causes.

In this study employing OCTA on patients with NAION, we observed statistically significant reductions in VD across the whole area, peripapillary region, and inferior segments when compared to both the fellow eye and healthy group in the microvascular examination of the OD. This cross-sectional analysis assessed the efficacy of OCTA in delineating peripapillary vascularity in non-acute, unilateral NAION cases. Notably, we restricted our study to NAION cases lasting more than 3 months because the acute phase is marked by disc edema and hemorrhage, potentially impeding imaging accuracy. Although OCTA enables excellent visualization of the microvascular structure of the OD and peripapillary region, its utility in these patients has not been clearly defined. OCTA imaging reflects changes in VD that can indicate functional impairment before irreversible structural changes. In a study by Spaide et al. (18), a comparison between OCTA images of healthy eyes' ODs and FFA revealed that the radial peripapillary capillary network was more effectively visualized in OCTA images, contrasting with its less clear visualization in FFA.

Higashiyama et al. (19) pioneered the observation of reduced retinal perfusion in an acute case of NAION using OCTA. OCTA clinical applications in patients with NAION have been further elucidated in several other studies evaluating retinal VD, choroid, and OD perfusion (20,12). Another study reported a significant decrease in OD perfusion in a prospective case series of patients with NAION (21). In a parallel investigation by Sharma et al. (22) encompassing six cases of acute NAION, the study revealed a reduction in both retinal and choroidal peripapillary VD. Notably, these findings may reflect distinct vascular changes influenced by the presence of disc edema and hemorrhages in NAION cases, potentially introducing variations in masking effects during imaging. In alignment with these observations, our study, using automated indices generated by the device software, also identified a reduction in peripapillary retinal VD. Peripapillary retinal VD and perfusion decrease in the peripapillary choriocapillaris have been reported in nine



cases of both acute and chronic NAION with an average duration of 23 months since the onset of the disease (23). Overall, OCTA VD patterns suggest a secondary watershed infarct hypothesis in NAION, possibly related to transient hypoperfusion or venous infarction (24). The decrease in microvascular connections associated with peripapillary tortuous capillaries detected in some cases may be consistent with the venous insufficiency hypothesis in NAION (22).

The analysis of the OCTA VD offers valuable quantitative insights. In patients with NAION, reductions in both the VD of the whole optic nerve area and the peripapillary region are observed compared to control subjects. These parameters hold promise as discerning indicators for distinguishing ischemic forms of OD edema from alternative etiologies. Future investigations should delve into distinct OCTA features and assess potential VD modifications in cases of inflammatory, infectious, and hypertensive acute OD edema. Such studies may pave the way for a more nuanced understanding of these conditions and contribute to the refinement of diagnostic approaches.

### Study Limitations

Although this study presents valuable insights, it is essential to acknowledge certain limitations. These include a restricted patient sample and confinement of the study to a single center. Nevertheless, it is crucial to note that OCTA stands out as a pioneering diagnostic tool, and NAION is an uncommon ocular disease. Despite these limitations, we contend that our documented cases offer valuable contributions to ophthalmologists in their clinical practice. Looking ahead, the expansion of case collection holds promise for a more comprehensive understanding of the diseases and may unveil diverse pathophysiologies associated with NAION. The prospect of larger screenings, coupled with improved visualization of the choriocapillaris through OCTA, can augment future investigations into choroidal microvasculature. It is worth mentioning that some OCTA images from certain patients were excluded because of motion artifacts. Anticipating advancements in software, particularly with the incorporation of real-time eye tracking, we are optimistic that this issue will be mitigated in future studies.

### Conclusion

In conclusion, OCTA is a repeatable, highly rapid, and non-invasive imaging method that can be used to detect VD defects in patients with NAION. In addition, it provides information about the vascular structures of the retina, choroid, and OD head using a short scan. If OCTA fails to yield a definitive diagnosis, more invasive and time-consuming

examination methods, such as FFA and indocyanine green angiography, can be subsequently employed.

### Ethics

**Ethics Committee Approval:** The study adhered to the principles of the Helsinki Declaration, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 3255, date: 27/04/2021).

**Informed Consent:** Retrospectively study.

### Authorship Contributions

Surgical and Medical Practices: D.Ö., M.K., D.Ç.Y., Concept: D.Ö., M.K., D.Ç.Y., Design: D.Ö., M.K., D.Ç.Y., Data Collection or Processing: D.Ö., M.K., D.Ç.Y., Analysis or Interpretation: D.Ö., M.K., D.Ç.Y., Literature Search: D.Ö., M.K., D.Ç.Y., Writing: D.Ö., M.K., D.Ç.Y.

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